# The Rajasthan Medical Journal

**Official Publication of the Medical and Health Department, Government of Rajasthan**
**Published by S.M.S. Medical College, Jaipur**

**Volume : 20** **ISSN : 0485-9561** **Issue 1 : January 2026**

## GUEST EDITORIAL

- When the Skin Speaks: Rash Recognition as a Patient Safety Priority

## ORIGINAL ARTICLE

- Mapping the 2024 Pharmacology CBME Curriculum in India: A Comparative Analysis of Competencies and Certification Requirements
- Evaluation of Radiation Dose in the most common Medical Imaging in a Pediatric Tertiary Care Hospital
- Comparative Analysis of Tanner Whitehouse-2 (TW2) and Tanner Whitehouse-3 (TW3) Methods for Forensic Skeletal Age Estimation in Adolescents (14–18 Years) in a tertiary care hospital
- Prevalence and Pattern of Psychoactive Substance Use among Undergraduate Medical Students in a Public Medical College of North India: A Cross-Sectional Study

## REVIEW ARTICLE

- Managing Dyslipidemia in 2026: Key Updates from the ACC/AHA Guideline for Clinical Practice
- Novel Oral Anticoagulants: – A Review on Clinical Evolution and Pharmacological Transition
- Transdiagnostic Neurobiological Mechanisms of Behavioral Addictions A Circuit Based Comparative Review
- Weight Regain and Cardiometabolic Reversal following Discontinuation of Incretin Based Therapies A Review

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## Guest Editorial

# When the Skin Speaks: Rash Recognition as a Patient Safety Priority

**Kanika Khandelwal***

**ABSTRACT**

Rashes are among the most common clinical findings encountered in inpatient care, yet they remain one of the most frequently underestimated. Often dismissed as benign, allergic, or "dermatological," rashes are instead a critical diagnostic window into systemic disease. Delayed or missed diagnosis of serious cutaneous manifestations represents an under-recognized patient safety issue, reflecting broader gaps in clinical prioritization, diagnostic reasoning, and hospital systems.

In an era increasingly focused on patient safety, quality of care, and diagnostic error, rash-related delays deserve explicit attention. The skin is not a peripheral organ. It is a visible, dynamic, and information-rich diagnostic surface, and failure to carefully assess its findings can result in preventable harm.

Many life-threatening conditions declare themselves initially through the skin. Stevens–Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), cutaneous vasculitis, meningococcemia, infective endocarditis, and necrotizing soft tissue infections may all present with early or subtle rashes. In such conditions, time to recognition often determines outcomes.

In busy inpatient settings, however, rashes are frequently deprioritized compared with laboratory abnormalities or radiologic findings. When patients present with fever, hypotension, sepsis, or organ dysfunction, skin findings may be relegated to secondary documentation, often described vaguely or without reassessment. This oversight allows critical diagnostic clues to be missed during early stages of illness.

Delayed diagnosis of rashes is rarely the result of a single error. Rather, it reflects predictable system-level vulnerabilities. Rashes are often described imprecisely, evolution over time is inadequately documented, and significant clinical overlap exists between infectious, inflammatory, and drug-related eruptions. Empiric treatments—particularly antibiotics and corticosteroids—may be initiated without timely diagnostic reconsideration. Dermatology consultation and skin biopsy both high-yield diagnostic tools, are frequently underutilized or sought late in the clinical course, reducing their diagnostic value.

The patient safety consequences of delayed rash recognition are substantial. Patients may experience progression to multi-organ dysfunction, prolonged hospitalization, unnecessary exposure to broad-spectrum antibiotics or immunosuppressive therapy, and increased risk of adverse outcomes. From a systems perspective, such delays increase length of stay, healthcare costs, and medicolegal risk. Importantly, many of these harms are preventable with earlier recognition and intervention.

These challenges are particularly relevant in Indian healthcare settings, including state and district hospitals across Rajasthan. High patient volumes, limited access to subspecialty consultation, and constrained resources amplify the impact of diagnostic delays. In such environments, improving bedside clinical recognition becomes even more critical. Early and accurate assessment of rashes can prevent unnecessary investigations, reduce inappropriate treatments, and optimize utilization of limited resources.

Reframing rash recognition as a patient safety priority represents a low-cost, high-impact opportunity for quality improvement. Structured skin examination, routine documentation of rash morphology and progression, early reassessment of treatment response, and lower thresholds for dermatology consultation or biopsy in high-risk presentations can meaningfully reduce diagnostic delays. Educational initiatives and simple inpatient algorithms that highlight red flags—such as mucosal involvement, necrosis, rapid progression, or systemic symptoms—can further support frontline clinicians.

Delayed diagnosis of rashes is not merely a dermatology issue; it is a cross-disciplinary patient safety concern. Addressing it requires cultural change, institutional support, and renewed emphasis on clinical observation as a core diagnostic skill. When recognized early, the skin often provides vital clues to underlying disease. Listening to those signals carefully can prevent harm, improve outcomes, and strengthen the quality of inpatient care.

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## Original Article

# Mapping the 2024 Pharmacology CBME Curriculum in India: A Comparative Analysis of Competencies and Certification Requirements

**Shivankan Kakkar*, Monica Jain**, Bikash Medhi*****


## ABSTRACT

Background: To map and compare the 2024 Pharmacology Competency-Based Medical Education (CBME) curriculum with the previous version, focusing on competencies, certification requirements, and the distribution across learning domains. This analysis aims to provide a framework for aligning institutional teaching with the new National Medical Commission (NMC) reforms.

Methods: A descriptive comparative document analysis of the 2024 NMC Pharmacology CBME curriculum and the previous 2018 MCI version was conducted. Ninety-two competencies from the revised curriculum were reviewed and compared with 64 from the earlier version. Each competency was analysed for its domain classification (Knowledge, Skill, Attitude, Communication), novelty (retained, modified, new), certification requirements, and suggested assessment methods (OSPE, DOAP, simulation). Data were analysed using descriptive statistics (frequency distribution and proportions).

Results: The 2024 curriculum introduces 17 certified competencies requiring mandatory logbook documentation. A significant shift towards the Attitude and Communication domains is evident. Notable additions include practical skills like prescription auditing, formal ADR reporting, communication training for counselling, and simulation-based management of emergencies. These changes reflect a move towards holistic, practice-oriented learning over theoretical knowledge.

Conclusion: The revised CBME curriculum in Pharmacology requires significant faculty preparedness in structured feedback, simulation-based teaching, and competency certification. The detailed mapping in this study provides a clear blueprint for institutions to effectively implement these critical NMC reforms.


Keywords: Competency-based medical education; Curriculum mapping; Patient safety; Rational drug use; Medical education reform.

## INTRODUCTION

Recent reforms in Indian medical education have repositioned the national curriculum to emphasize clinical relevance, ethical prescribing, and patient safety. These reforms are embodied in the Competency-Based Medical Education (CBME) framework introduced by the National Medical Commission (NMC), which aims to produce clinicians who are skilled, communicative, and contextually aware from their undergraduate years onward.

On 12 September 2024, the NMC released a revised Pharmacology CBME curriculum, set to be implemented uniformly across India starting with the MBBS batch of 2024. The updated framework prioritizes application over memorization and mandates certification of key clinical skills, rational prescription planning, adverse drug reaction (ADR) reporting, and patient communication.

The previous curriculum, designed under the aegis of the Medical Council of India, focused predominantly on theoretical and cognitive outcomes. Although it included pharmacotherapeutics and drug safety, these were primarily lecture-based and sparsely assessed in practice.

Faculty members are now tasked with facilitating demonstrable competencies categorized under four domains—Knowledge (K), Skills (S), Attitude (A), and Communication (C). Simulations, computer-assisted learning (CAL), DOAP (Demonstrate, Observe, Assist, Perform) sessions, and role-plays are now central to pharmacology education. Emphasis is also being placed on structured assessment formats like OSPE (Objective Structured Practical Examination) and structured logbook documentation.

This manuscript serves as a comparative guide, offering a competency-level analysis between the old and new curricula, identifying certification-ready components, and proposing practical steps for institutional implementation.

## METHODS

**Design:** Descriptive comparative document analysis.

**Data Sources:**

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- 2018 Pharmacology Curriculum (MCI).
- NMC modules on Assessment and Alignment & Integration.
- Supplementary literature on CBME implementation frameworks.

**Methodology**:

A manual mapping of all 92 competencies in the 2024 Pharmacology curriculum was conducted across 10 subject-wise topics and compared with 64 competencies from the earlier curriculum. Each competency was classified using the following criteria:

- Domain (Knowledge [K], Skill [S], Attitude [A], Communication [C])
- Type (Retained, Modified, New, or Discontinued)
- Certification status (Yes/No)
- Type of pedagogical/assessment strategy involved (OSPE, DOAP, simulation, CBL)
- Feasibility for logbook-based certification

**Ethical Considerations**:

No human subjects were involved. The content is drawn from publicly accessible curriculum documents and qualified as documentary analysis.

**Statistical Methods:**

- This study is descriptive in nature.
- All results are presented using frequencies, tables, and categorical comparisons.
- Descriptive labels included: Retained, Modified, New, and Discontinued.
- No inferential statistics, p-values, or confidence intervals were computed.
- Data is presented to support implementation-level decision-making rather than hypothesis testing.

**RESULTS**

**Key Highlights**:

- Out of 92 total competencies, 17 require formal certification and logbook documentation.
- Over 35% of competencies involve some practical, case-based, or observational activity.
- Simulation and Role-play were introduced in key domains: poisoning, contraception counselling, OTC drug use, and adherence.
- Attitude (A) and Communication (C) domains are now individually assigned in multiple competencies compared to implicit references in the older curriculum.

**Topic 1: General Pharmacology**

The previous curriculum addressed most core principles of pharmacology (PH1.1 to PH1.11). The new curriculum builds upon this by adding certification for drug formulations and routes of administration (PH1.4, PH1.5), introduces mechanism of action via CAL (PH1.8), and formalizes adverse drug reaction (ADR) reporting under pharmacovigilance (PH1.12). Labelling, classification, and cost-effectiveness of drug nomenclature is also emphasized (PH1.3).

**Table 1: General Pharmacology**

Total Competencies: 13 | Certifications Required: 4

| PH Code | Competency Description | Present in Old Curriculum | Status | Practical Component | Certification Required |
|---|---|---|---|---|---|
| PH1.1 | Principles and terminology of pharmacology | Yes | Modified | No | No |
| PH1.2 | Evidence-based medicine and rational use | Yes | Modified | No | No |
| PH1.3 | Nomenclature (generic, branded, scheduled) | Partial | Modified | Yes | No |
| PH1.4 | Formulations and delivery systems | Yes | Modified | Yes (DOAP, OSPE) | Yes |
| PH1.5 | Routes of administration | Yes | Modified | Yes (DOAP, Simulation) | Yes |
| PH1.6 | ADME and relation to drug routes | Yes | Modified | Yes (Graphs, Simulation) | No |
| PH1.7 | Mechanism of action | Yes | Retained | Yes (Demo) | No |
| PH1.8 | CAL: Mechanism demonstration via software | No | New | Yes (CAL) | Yes |
| PH1.9 | Rational combinations (PK/PD) | No | New | Yes (CBL) | No |
| PH1.10 | Special situations (pediatrics, geriatrics, etc.) | Partial | Modified | Yes (CBL) | No |
| PH1.11 | ADR types and causality | Partial | Modified | Yes (OSPE) | No |
| PH1.12 | Pharmacovigilance and ADR reporting | Yes (limited) | Modified | Yes (Form filling) | Yes |
| PH1.13 | Drug interactions, management and audit | Partial | Modified | Yes (Rx audit) | Yes |

**Figure 1.** General Pharmacology (Descriptive Statistics).

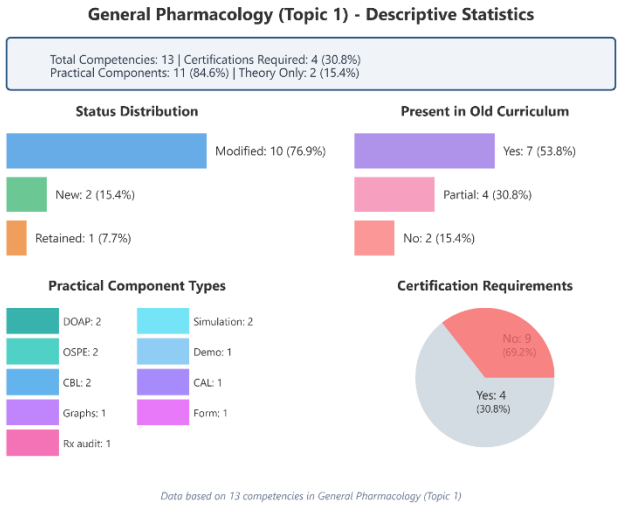
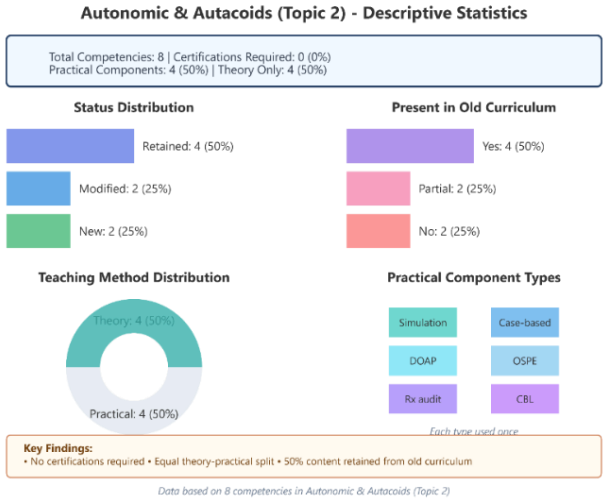



**Figure 2.** Autonomic & Autacoids (Descriptive Statistics).




### Topic 2: Autonomic and Autacoids

This topic is expanded to include the simulation of emergencies involving adrenergic and cholinergic drugs (PH2.2, PH2.3). Skill-based demonstrations such as the use of local anaesthetics (PH2.5) are integrated with case-based and DOAP sessions. Traditional knowledge areas (types, PK/PD, uses) are retained.

### Table 2: Autonomic and Autacoids

Total Competencies: 8 | Certifications Required: 0

| PH Code | Competency Description | Present in Old Curriculum | Status | Practical Component | Certification Required |
|---|---|---|---|---|---|
| PH2.1 | Adrenergic/anti-adrenergic drugs | Yes | Retained | No | No |
| PH2.2 | Cholinergic/anticholinergic + OPC poisoning | Partial | Modified | Yes (Simulation) | No |
| PH2.3 | Emergency use of sympathomimetics | No | New | Yes (Case-based) | No |
| PH2.4 | Skeletal muscle relaxants | Yes | Retained | No | No |
| PH2.5 | Local anaesthetics + demonstration | Partial | Modified | Yes (DOAP, OSPE) | No |
| PH2.6 | Antihistamines and cold/allergy mgmt. | Yes | Retained | No | No |
| PH2.7 | Pain, NSAIDs (excluding opioids) | Yes | Retained | No | No |
| PH2.8 | Gout, arthritis, migraine management plan | No | New | Yes (Rx audit, CBL) | No |

### Topic 3: Central Nervous System

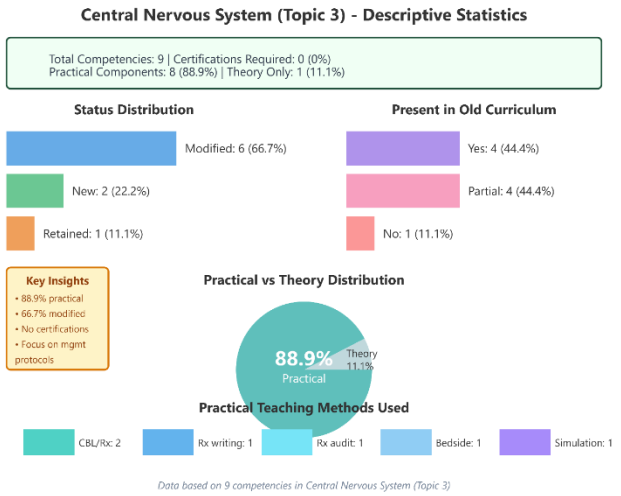
This section includes expanded competencies on epilepsy, psychiatric disorders, alcohol and opioid management. Benzodiazepine and neurodegenerative disorder treatment plans are application-focused. Prescription writing, case-based discussions, and bedside teaching are emphasized across most CNS topics.

### Table 3: Central Nervous System

Total Competencies: 9 | Certifications Required: 0

| PH Code | Competency Description | Present in Old Curriculum | Status | Practical Component | Certification Required |
|---|---|---|---|---|---|
| PH3.1 | General anaesthetics and premedication | Yes | Retained | No | No |
| PH3.2 | Sedatives/hypnotics + selection rationale | Partial | Modified | Yes | No |
| PH3.3 | Epilepsy drugs + uncontrolled seizure mgmt. | Partial | New | Yes (CBL/Rx) | No |
| PH3.4 | Opioids and safe use protocols | Yes | Modified | Yes | No |
| PH3.5 | Depression and psychosis Mgmt. plan | Partial | Modified | Yes (Rx writing) | No |
| PH3.6 | Anxiety pharmacotherapy + goals | No | New | Yes | No |
| PH3.7 | Parkinsonism, Rx for drug-induced types | Partial | Modified | Yes (Rx audit) | No |
| PH3.8 | Methanol/ethanol poisoning | Yes | Modified | Yes (bedside/CBL) | No |
| PH3.9 | Drug abuse and de-addiction steps | Yes | Modified | Yes (Simulation) | No |

**Figure 3.** Central Nervous System (Descriptive Statistics).




## Topic 4: Cardiovascular System and Blood

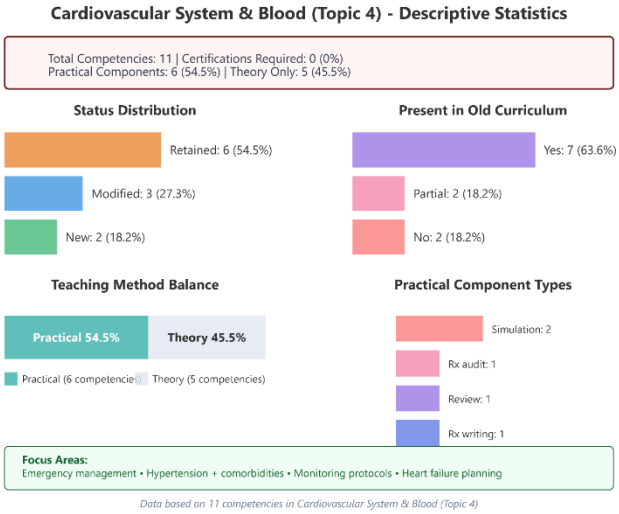
This section covers hypertension management (PH4.7), arrhythmia control, coagulation monitoring (PH4.2), and heart failure planning (PH4.9). Case simulations and bedside decision-making are prioritized although there is no mandatory certification listed.

**Table 4: Cardiovascular System & Blood**

Total Competencies: 11 | Certifications Required: 0

| PH Code | Competency Description | Present in Old Curriculum | Status | Practical Component | Certification Required |
|---|---|---|---|---|---|
| PH4.1 | Drugs for anaemia and thrombocytopenia | Yes | Retained | Yes (Rx audit) | No |
| PH4.2 | Anticoagulants + monitoring | Partial | Modified | Yes (Review) | No |
| PH4.3 | Fibrinolytics and antifibrinolytics | Yes | Retained | No | No |
| PH4.4 | Antiplatelet agents | Yes | Retained | No | No |
| PH4.5 | Diuretics and vasopressin | Yes | Retained | No | No |
| PH4.6 | RAAS inhibitors | Yes | Retained | No | No |
| PH4.7 | Hypertension + DM/PIH/emergency cases | No | New | Yes (Simulation, Rx writing) | No |
| PH4.8 | IHD and MI management plan | Partial | Modified | Yes | No |
| PH4.9 | Management plan for heart failure | Yes | Modified | Yes | No |
| PH4.10 | Arrhythmias and cardiac arrest | No | New | Yes (Simulation) | No |
| PH4.11 | Dyslipidaemia and causative drugs | Yes | Retained | No | No |

**Figure 4.** Cardiovascular System & Blood (Descriptive Statistics).




## Topic 5: Respiratory System

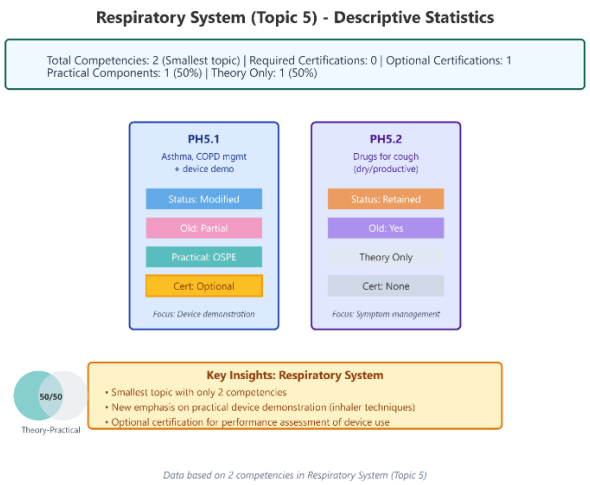
There is a new emphasis on practical device use (simulation, OSPE) for asthma and COPD (PH5.1), requiring performance assessment for inhaler demonstration. Earlier content focused solely on theoretical management of respiratory conditions.

**Table 5: Respiratory System**

Total Competencies: 2 | Certifications Required: 0

| PH Code | Competency Description | Old Coverage | Status | Practical | Certification |
|---|---|---|---|---|---|
| PH5.1 | Asthma, COPD mgmt. + device demo | Partial | Modified | Yes (OSPE) | Optional |
| PH5.2 | Drugs for cough (dry/productive) | Yes | Retained | No | No |

**Figure 5.** Respiratory System (Descriptive Statistics).



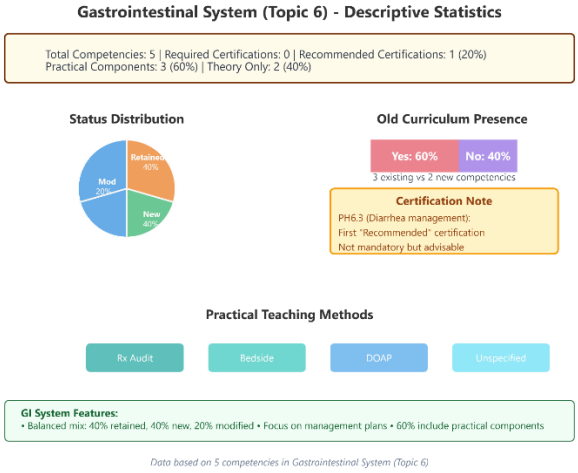

## Topic 6: Gastrointestinal System

New competencies related to case-based management of GERD, diarrheal diseases, and constipation have been added. Teaching must emphasize clinical therapy planning.

**Table 6: Gastrointestinal System**
Total: 5 Competencies | Certifications Required: Optional (PH6.3 advisable)

| PH Code | Competency Description | Present in Old Curriculum | Status | Practical Component | Certification Required |
|---|---|---|---|---|---|
| PH6.1 | Peptic ulcer/GERD Rx plan | Yes | Modified | Yes (Rx Audit) | No |
| PH6.2 | Antiemetics and prokinetics | Yes | Retained | No | No |
| PH6.3 | Diarrhoea management (child + adult) | No | New | Yes (bedside, DOAP) | Recommended |
| PH6.4 | Constipation management | No | New | Yes | No |
| PH6.5 | IBD/IBS drug therapy | Yes | Retained | No | No |

**Figure 6.** GI System (Descriptive Statistics).




## Topic 7: Endocrine System

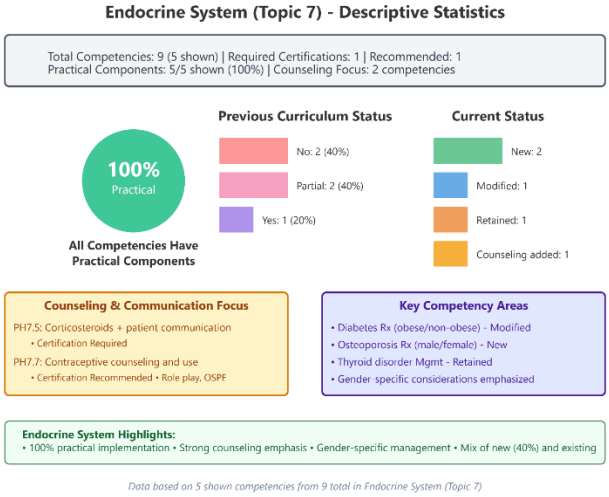
Key additions include separate management plans for obese and non-obese diabetics (PH7.1), prescription and counselling on contraceptives (PH7.7), and cautionary instructions for corticosteroid use (PH7.5).

**Table 7: Endocrine System**
Total Competencies: 9 | Certifications Required: 1 (Counselling)

| PH Code | Competency Description | Previous Status | Changes | Practical | Certification |
|---|---|---|---|---|---|
| PH7.1 | Diabetes Rx (obese/non-obese) | Partial | Modified | Yes | No |
| PH7.2 | Osteoporosis Rx (male/female) | No | New | Yes | No |
| PH7.3 | Thyroid disorder Mgmt. | Yes | Retained | Yes | No |
| PH7.5 | Corticosteroids + patient communication | Partial | Counselling added | Yes | Yes |
| PH7.7 | Contraceptive counselling and use | No | New | Yes (Role play, OSPE) | Yes recommended |

*Others like PH7.4, PH7.6, PH7.8, PH7.9 are retained or new but not associated with certification.*

**Figure 7.** Endocrine System (Descriptive Statistics).



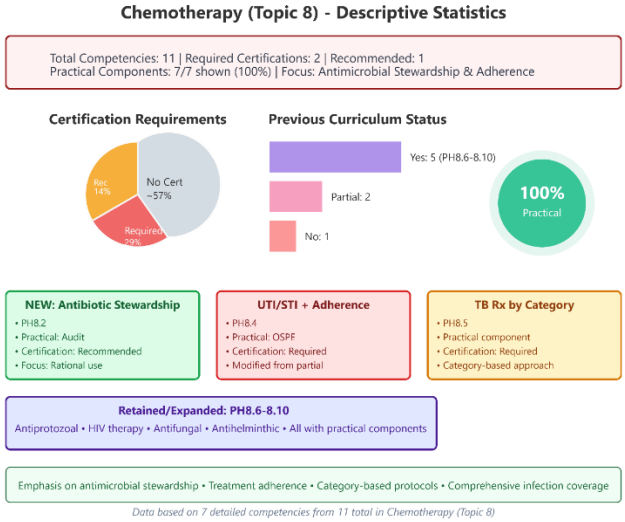

## Topic 8: Chemotherapy

This topic incorporates antimicrobial stewardship (PH8.2), logical antibiotic usage, leprosy, malaria, helminthiasis, and viral disease therapy. Simulated role-play, prescription audit, and counselling skills are key strategies.

**Table 8: Chemotherapy**
Total Competencies: 11 | Certifications Required: 2

| PH Code | Competency | Present Before | Change | Practical | Certification |
|---|---|---|---|---|---|
| PH8.2 | Antibiotic Stewardship | No | New | Yes (Audit) | Recommended |
| PH8.4 | UTI/STI Rx plans + adherence | Partial | Modified | Yes (OSPE) | Yes |
| PH8.5 | TB Rx by category | Partial | Modified | Yes | Yes |
| PH8.6–8.10 | Antiprotozoal, HIV, fungal, helminths | Yes | Retained / Expanded | Yes | No |

**Figure 8.** Chemotherapy (Descriptive Statistics).



### Topic 9: Miscellaneous

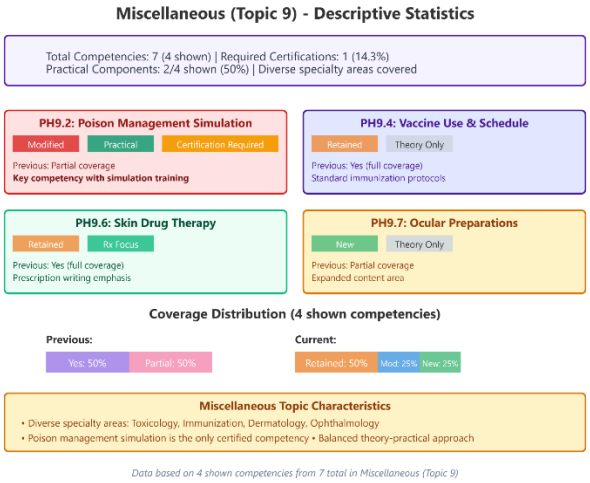
This section details rare yet essential competencies including drug use in poisoning, pesticide exposure, vaccination basics, antiseptics, and sunscreen/skin drug use.

**Table 9: Miscellaneous**

Total Competencies: 7 (4 shown) | Certifications Required: 1

| PH Code | Competency | Covered Previously | Status | Practical | Certification |
|---|---|---|---|---|---|
| PH9.2 | Poison management simulation | Partial | Modified | Yes | Yes |
| PH9.4 | Vaccine use & schedule | Yes | Retained | No | No |
| PH9.6 | Skin drug therapy | Yes | Retained | Rx focus | No |
| PH9.7 | Ocular preparations | Partial | New | No | No |

**Figure 9.** Miscellaneous (Descriptive Statistics).




### Topic 10: Applied Pharmacology

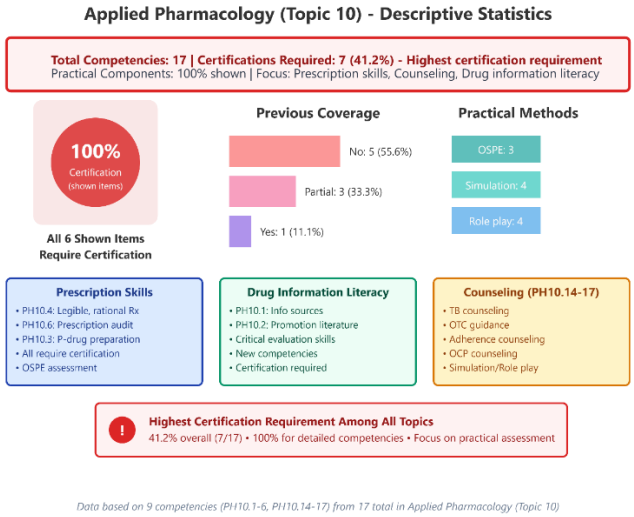
The most structured set of practical expectations is in this section. Students must write and justify at least 5 prescriptions (PH10.4), critically audit prescriptions (PH10.6), demonstrate patient counselling skills (PH10.14–PH10.17), submit P-drug lists (PH10.3), and fill and evaluate ADR forms (PH1.12, PH10.13). This section integrates concepts of Pharmacoeconomics, legal prescribing, over-the-counter medication counselling, and communication–making it the centrepiece of assessment.

**Table 10: Applied Pharmacology**

Total: 17 Competencies | Certifications Required: 7

| PH Code | Competency | Previously Covered | Changes | Practical | Certification Code |
|---|---|---|---|---|---|
| PH10.1 | Drug info sources comparison | No | New | Yes | PH10.1 |
| PH10.2 | Drug promotion literature | Partial | Modified | Yes (OSPE) | PH10.2 |
| PH10.3 | P-drug preparation | Partial | Structured | OSPE | PH10.3 |
| PH10.4 | Legible, rational prescription (5) | Yes | Added certification | Yes | PH10.4 |
| PH10.6 | Prescription audit | Partial | Refined | OSPE | PH10.6 |
| PH10.14 – PH10.17 | Counselling on TB, OTC, adherence, OCP | No | New | Simulation /Role play | PH10.14–PH10.17 |

**Figure 10.** Applied Pharmacology (Descriptive Statistics).




## DISCUSSION

The recently launched 2024 CBME Pharmacology curriculum marks a pivotal shift in Indian medical education—moving from passive cognitive learning to outcome-oriented, competency-certified education. This change is strongly aligned with global best practices that promote early professional identity formation and patient-centred prescribing behaviour.

This review shows a greater emphasis on simulation, active assessment (OSPE, DOAP), and interprofessional collaboration. Core competencies from the older content are retained but are now linked with clinical contexts—for example, learning about anti-epileptic drugs now requires students to manage a simulated seizure emergency. Similarly, ADR form filling and prescription auditing are no longer ancillary activities but integral components assessed for certification.

Major implementation challenges include:

- Faculty training in running OSPEs and simulations
- Availability of infrastructure like smart drug information systems, CAL software, or mock prescription labs
- Time allocation and scheduling for performing, observing, and recording certifications
- Faculty-student documentation load especially concerning logbook standardization

Faculty development workshops with standard case scenarios, calibration of OSPE stations, and digitized logbooks will be essential for equitable implementation. Furthermore, institutional alignment—especially vertically and horizontally across clinical departments—is vital for pharmacology topics that overlap with medicine, psychiatry, gynaecology, and pediatrics.

## CONCLUSION

The CBME 2024 curriculum for Pharmacology is a remarkable transformation in undergraduate (UG) medical education in India - placing competency and ethics at the centre of pharmacology teaching. With seventeen certifiable competencies, strong skill emphasis, and competency-based assessment, the subject is more clinically engaging and aligned with practical healthcare delivery.

Medical colleges and faculty must treat this not as a curricular update, but as a systemic change - demanding capacity building, integration, and technology adoption. This paper provides a structured guide for planning and executing the curriculum beginning with the MBBS batch of 2024–25, serving as a blueprint for course coordinators, educators, and curriculum regulators.

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## AVAILABILITY OF DATA AND MATERIALS

Data will be available by emailing shivankankakkar@rajasthan.gov.in

## AUTHORS' CONTRIBUTIONS

- Author*: participated in the investigation, methodology, resources, supervision, validation, writing, reviewing, and editing.
- Author**: participated in the conceptualization, writing, review, and editing.
- Author***: corresponding author participated in reviewing, and editing.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

## COMPETING INTEREST

The authors declare that they have no competing interests.

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## Original Article

# Evaluation of Radiation Dose in the most common Medical Imaging in a Pediatric Tertiary Care Hospital

**Ajay Prajapati*, Anu Bhandari**, Arun Chougule*****


## ABSTRACT

**Background:** Pediatric patients (PPs) require special care during medical imaging procedures because they are more vulnerable to radiation-induced effects than adults. The objective of this study is to optimize the radiation exposure without compromising image quality and enhancing patient safety during the radiological imaging of PPs.
**Methods:** This study was performed on 215 PPs under the age of 15 years, who were clinically referred for medical imaging, and the Entrance Surface Dose (ESD) was measured using a DAP meter during radiological imaging of eight most commonly examined body regions.
**Results:** This study revealed that the chest lateral x-ray projection exhibited the lowest mean ESD of 0.07 mGy·cm² in the 0–1 year age group, whereas the highest dose of 0.79 mGy·cm² was observed for the lumbar spine lateral view in the 10–15-year age group
**Conclusion:** This study facilitates evaluation of effective ESD using the DAP meter, supporting the establishment of DRLs and enhancing image quality while reducing radiation exposure.


**Keywords:** Entrance surface dose, Pediatric patients, Dose reference levels, DAP meter, Optimising radiation dose.

## INTRODUCTION

Radiation, whether natural or artificial, propagates across a medium in the form of waves and particles. Medical practitioners use x-rays, the predominant form of artificial radiation, for the diagnosis and treatment of patients. Although these x-rays are useful to diagnose and treat the patients, on the other hand, they also emit some amount of energy that may adversely affect essential biological elements, including DNA, possibly resulting in detrimental consequences. These radiation effects have been acknowledged by the International Commission on Radiological Protection (ICRP), which has recommended that all X-ray procedures adhere to prescribed radiation dosage limits.

Medical imaging plays a key role in diagnosing medical conditions and is commonly used for patients of all ages, including children. When a child is referred for such imaging or treatment, they are considered a pediatric patient. Pediatric patients (PPs) are not merely scaled-down versions of adults, as their bodies undergo significant developmental changes throughout infancy and adolescence. To ensure appropriate care, they are categorized by age groups: neonates (0–28 days), infants (28 days to 1 year), toddlers (13 months to 2 years), children (2–12 years), early adolescents (12–18 years), and late adolescents (19–21 years).

PPs require more precautions during medical imaging in order to achieve high-quality radiographs while lowering radiation hazards because they are more radiation-sensitive than adults. International organizations have focused on three key principles to accomplish this: justification, optimization, and dose limitation. In addition, they have established reference dose guidelines tailored for both adult and pediatric populations. The amount of radiation received by PPs can differ based on their physical characteristics, such as age, height, weight, and body thickness, as well as the specific exposure settings, including kVp, mAs, and distance. As a result, it is important to assess each exposure to determine the Entrance Surface Dose (ESD) or establish Dose Reference Levels (DRLs).

Various methods exist for evaluating ESD, but one commonly used tool is the DAP meter. This device measures the total radiation exposure by considering both the dose and the area of tissue exposed. The DAP meter expresses reading in Gray +square meters (Gy·m²) and does not vary with the distance between the x-ray source and the patient's surface. Instead, it is influenced by factors such as the applied kilovoltage (kVp), milliampere-seconds (mAs), and the size of the radiation field. In different imaging systems—such as conventional radiography, computed radiography (CR), and digital radiography (DR)—DAP values can vary even when the same exposure settings or imaging techniques are used.

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## MATERIAL AND METHODS

This research received ethical clearance from the Ethics Committee of SMS Medical College and Attached Hospitals, Jaipur (Reference No: 731/MC/EC/2023). It was carried out at JK Lone Hospital between August 2023 and June 2024. Prior to initiating the study, quality assurance (QA) and quality control (QC) procedures were implemented in accordance with the Atomic Energy Regulatory Board (AERB) guidelines for the computed radiography (CR) x-ray system. The output (O/P) of the x-ray tube was measured to be 0.93 mGy/mAs, and to calculate the ESD, the entrance surface air kerma was estimated using the tube output with the following formula.

ESD = (O/P) x 〖(kVp/80)〗^(2 )x (mAs) x 〖(100/FSD)〗^(2 )x (BSF)

The tube output was assessed along the central axis of the x-ray beam at a distance of 100 cm from the tube's focal spot. The mAs value was calculated by multiplying the exposure time by the tube current, and the kVp indicates the maximum voltage applied during each radiographic examination. The focus-to-skin distance (FSD) refers to the measurement between the x-ray tube's focal point and the surface of the patient. A backscatter factor (BSF) of 1.35 was utilized in this study.

A total of 215 pediatric patients under the age of 15 were randomly selected for this study, all of whom had been referred for radiological imaging by their physicians. There were 98 female patients and 117 male patients among these individuals. Data collected included the patients' physical characteristics (age, sex, and weight) as well as the exposure parameters used during imaging (kVp, mAs, and distance). For dose estimation and data analysis, eight different medical imaging projections were examined: chest (AP/Lateral), flat plate abdomen (FPA), lumbar spine (AP/Lateral), pelvis (AP), and skull (AP/Lateral).

Accurate radiation doses were determined using a DAP meter (KERMAX-Plus SDP, model 120-210), capable of measuring x-ray output within an energy range of 40 to 150 kVp. The device functions under environmental conditions that include temperatures from -20°C to +50°C, relative humidity between 10% and 90% (non-condensing), and atmospheric pressures from 500 to 1062 hPa. The system comprises an ionization chamber and a connected DAP reader. The chamber was positioned beneath the collimator and connected to the reader via a cable, allowing dose measurements to be displayed within 1 to 3 seconds. Radiation doses were initially recorded in Gy·m² and later converted to Gy·cm² for further analysis and comparison.

## RESULTS

In this study, the findings were assessed based on radiographic parameters through a combination of descriptive statistics and qualitative analysis. Data from each radiological procedure were examined using statistical measures such as the first and third quartiles, mean, standard deviation, as well as minimum and maximum values. Table 1 provides a summary of the radiographic and demographic information, including x-ray projection types, patient age and weight, and the exposure settings used (mAs and kVp), along with their corresponding average ranges.

Table 1: Displays radiological and patient parameters together with their averages and ranges. The radiological parameters help to calculate the dose, and patient parameters help to calculate the BMI and body separation.

| S. No | Projection | Number | Age (year) | Sex | Patient Weight (Kg) | mAs | Total Voltage (kVp) |
|---|---|---|---|---|---|---|---|
| 1. | Chest - AP | 59 | 2.37 (1 day-5 years) | 21 (F), 38 (M) | 10.83 (1.5-40) | 9.05 (6-13) | 57.69 (48-65) |
| 2. | Chest - Lat | 21 | 0.8 (0 day - 1 year) | 10 (F), 11 (M) | 2.47 (1.5-4.5) | 8.2 (6-13) | 56.87 (55-58) |
| 3. | FPA | 28 | 6.16 (2 days-10 years) | 18 (F), 10 (M) | 12.6 (2.5-30) | 11.58 (6-16) | 60.58 (55-64) |
| 4. | L S spine - AP | 13 | 13.67 (10 years-15 years) | 5 (F), 8 (M) | 27.083 (18-35) | 18.16 (16-25) | 63.16 (58-68) |
| 5. | L S spine - Lat | 28 | 7.64 (1 year-15 years) | 12 (F), 16 (M) | 17.5 (5-36) | 18 (13-25) | 63.09 (58-70) |
| 6. | Pelvis | 15 | 7.80 (1 year-15 years) | 9 (F), 6 (M) | 17.2 (3-28) | 9.6 (6-13) | 59.46 (56-62) |
| 7. | Skull - AP | 29 | 3.69 (4 days-10 years) | 13 (F), 16 (M) | 8.18 (2.5-18) | 10.08 (6-16) | 59.36 (56-68) |
| 8. | Skull - Lat | 22 | 4.86 (15 days-10 years) | 10 (F), 12 (M) | 11.41 (3-26) | 9.68 (6-13) | 59.91 (5-68) |

The DAP meter readings are presented in Table 2. Among the recorded values, the lowest third quartile value, 0.07 mGy·cm², was observed in the lateral chest projection for patients aged 0 to 1 year. In contrast, the highest third quartile value, 0.89 mGy·cm², was noted for the lateral lumbar spine projection in the 10 to 15-year age group. As shown in Table 3, the DAP measurements from this study are more closely aligned with recent findings compared to

earlier studies. Figure 1 provides a visual comparison of the current DAP results with those from related research.

Table 2: Displays the average, minimum, maximum, mean, median, first quartile, third quartile, and maximum to minimum ratio of the DAP meter for X-ray examination.

| S. No | Projection | Number | Age (year) | Sex | Patient Weight (Kg) | mAs | Total Voltage (kVp) |
|---|---|---|---|---|---|---|---|
| 1. | Chest - AP | 59 | 2.37 (1 day-5 years) | 21 (F), 38 (M) | 10.83 (1.5-40) | 9.05 (6-13) | 57.69 (48-65) |
| 2. | Chest - Lat | 21 | 0.8 (0 day - 1 year) | 10 (F), 11 (M) | 2.47 (1.5-4.5) | 8.2 (6-13) | 56.87 (55-58) |
| 3. | FPA | 28 | 6.16 (2 days-10 years) | 18 (F), 10 (M) | 12.6 (2.5-30) | 11.58 (6-16) | 60.58 (55-64) |
| 4. | L S spine - AP | 13 | 13.67 (10 years-15 years) | 5 (F), 8 (M) | 27.083 (18-35) | 18.16 (16-25) | 63.16 (58-68) |
| 5. | L S spine - Lat | 28 | 7.64 (1 year-15 years) | 12 (F), 16 (M) | 17.5 (5-36) | 18 (13-25) | 63.09 (58-70) |
| 6. | Pelvis | 15 | 7.80 (1 year-15 years) | 9 (F), 6 (M) | 17.2 (3-28) | 9.6 (6-13) | 59.46 (56-62) |
| 7. | Skull - AP | 29 | 3.69 (4 days-10 years) | 13 (F), 16 (M) | 8.18 (2.5-18) | 10.08 (6-16) | 59.36 (56-68) |
| 8. | Skull - Lat | 22 | 4.86 (15 days-10 years) | 10 (F), 12 (M) | 11.41 (3-26) | 9.68 (6-13) | 59.91 (5-68) |

Table 3: Display of the results of this study is the close alignment of its DRL values with those reported in earlier studies by comparing them.

| S. No. | Projection | Age (Year) | This Study | UK[a] - 2009 | India[b]- 2011 | USA[c]- 2012 | Germany[d]- 2019 |
|---|---|---|---|---|---|---|---|
| 1. | Chest-AP | 0-1 | 0.16 | 0.10 | 0.07 | 0.12 | 0.08 |
| | | 1-5 | 0.24 | 0.12 | 0.09 | 0.14 | 0.10 |
| 2. | Chest - Lat | 0-1 | 0.07 | 0.13 | 0.14 | 0.15 | 0.12 |
| 3. | FPA | 0-1 | 0.40 | 0.30 | 0.33 | 0.35 | 0.32 |
| | | 1-5 | 0.44 | 0.35 | 0.37 | 0.38 | 0.36 |
| 4. | L S spine - AP | 10-15 | 0.61 | 1.00 | 1.10 | 1.10 | 1.05 |
| 5. | L S spine - Lat | 1-5 | 0.48 | 1.10 | 1.20 | 1.25 | 1.15 |
| | | 5-10 | 0.42 | 1.15 | 1.25 | 1.30 | 1.20 |
| | | 10-15 | 0.89 | 1.20 | 1.30 | 1.35 | 1.25 |
| 6. | Pelvis | 1-5 | 0.18 | 0.50 | 0.55 | 0.55 | 0.52 |
| | | 10-15 | 0.41 | 0.60 | 0.65 | 0.65 | 0.62 |
| 7. | Skull - AP | 0-1 | 0.29 | 0.28 | 0.32 | 0.30 | 0.29 |
| | | 1-5 | 0.43 | 0.32 | 0.35 | 0.35 | 0.33 |
| | | 5-10 | 0.53 | 0.36 | 0.40 | 0.40 | 0.38 |
| 8. | Skull – Lat | 0-1 | 0.34 | 0.35 | 0.38 | 0.40 | 0.36 |
| | | 5-10 | 0.45 | 0.45 | 0.50 | 0.50 | 0.46 |

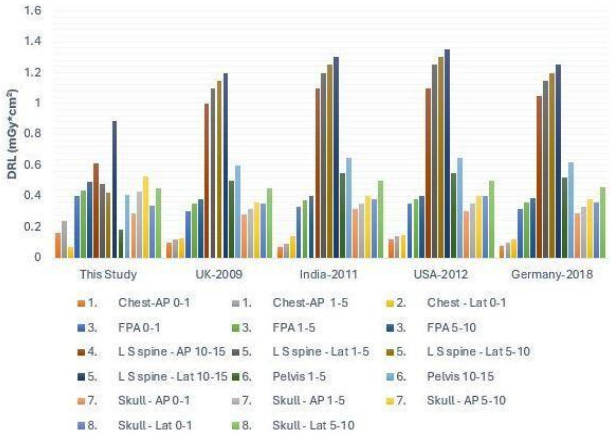
a Hart D. et al., 2009.

b Sonawane A. U. et al., 2011.

c Brink J.A. et al., 2012

d Schegerer, A. et al., 2019,

Figure 1: The bar graph compares the DRL values from this study to those from the UK in 2009, India in 2011, the USA in 2012, and Germany in 2019. In such studies, the DRL values are typically lower, except for Chest-AP, Chest-Lateral, and FPA.




## DISCUSSION

PPs are particularly vulnerable to the effects of radiation due to their developing stage, and extensive use of x-rays can damage DNA, resulting in mutations, long-term radiation-induced conditions, and cancer. At present, the treatment of cancer is a mystery, but scientists are currently investigating a wide range of potential avenues to uncover the truth. Thus, measuring the ESD is crucial to guarantee the safety of patients undergoing medical examinations. This study evaluates the ESD for eight different x-ray projections in patients aged from birth to 15 years. The calculations incorporated various radiological and patient-specific factors, excluding height, as detailed in Table 1. Unlike previous research that relied on a limited set of formulas and projections and frequently included Body Mass Index (BMI), this method provided a more thorough evaluation.

The European Commission recommends using tube voltage settings between 60 and 80 kVp for infants aged 0 to 1 year, and between 100 and 120 kVp for children aged 5 years and older. Previous studies have advised against using tube voltages below 60 kVp for pediatric imaging. In contrast, this study found that the average tube voltage for children aged 0 to 15 years ranged from 55.60 to 63.16 kVp. Although earlier practices often favored high mA and low kilovolt kV settings, advancements in X-ray technology and improved technologist expertise now allow for more effective mA-

kV combinations, enabling high-quality imaging with optimum radiation exposure.

To precisely assess the ESD in pediatric, a DAP meter was used simultaneously during medical imaging procedures, without modifying any radiological or patient-specific settings. The lowest third quartile DAP value observed was 0.07 mGycm² for a chest lateral projection in the 0–1-year age group, while the highest was 0.89 mGycm² for a lumbar spine lateral projection in the 10–15-year age group. The data collected using the DAP meter were compared with findings from other studies involving the eight most frequently performed X-ray projections in children aged 0 to 15 years. The DRL values in this study were slightly elevated for chest-AP, chest-lateral, and FPA projections. Conversely, DRL values for LS Spine-AP, LS Spine-Lateral, Pelvis-AP, Skull-AP, and Skull-Lateral were significantly lower compared to those reported in studies from the UK (2009), India (2011), the USA (2012), and Germany (2019). These differences may be due to several variables, including patient sample size, selected kVp and mAs values, collimation practices, FSD, equipment type, and the imaging techniques used by radiologic technologists.

The findings of this study align well with previously published research and play a key role in optimizing patient radiation exposure without compromising image quality. The ESD can be reduced by conducting regular QA and quality QC checks of imaging equipment, providing ongoing training and refresher courses for radiologic technologists, adhering to established DRLs and regulatory guidelines, using suitable immobilization tools for pediatric patients, and effectively managing the work schedules of radiation staff to minimize errors and improve performance.

## CONCLUSION

This research approach makes it possible to evaluate ESD effectively utilizing the DAP meter, a reliable scientific tool for accurate ESD assessment. This DAP meter data is essential in determining DRLs and evaluating ESD across an organization, which helps enhance image quality while optimizing radiation exposure.

## ABBREVIATIONS

| | |
|---|---|
| PPs | Pediatric Patients |
| ICRP | International Commission on Radiation Protection |
| QA | Quality Assurance |
| QC | Quality Control |
| ESD | Entrance Surface Dose |
| DRLs | Dose Reference Levels |
| DAP | Dose Area Product |
| TLD | Thermoluminescence Dosimeter |
| CR | Computed Radiography |
| DR | Digital Radiography |
| AERB | Atomic Energy Regulatory Board |
| KVp | Peak kilovolts |
| mAs | Milliampere-seconds |
| FSD | Film to Source Distance |
| NRPB | National Radiation Protection Board |
| BSF | Backscatter factor |
| AP | Anterior to Posterior |
| PA | Posterior to Anterior |
| FPA | Flat Plate Abdomen |
| KUB | Kidney Ureter Bladder |
| FSD | Focus to Skin Distance |

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## AVAILABILITY OF DATA AND MATERIALS

Data will be available by emailing at rttajay@gmail.com

## AUTHORS' CONTRIBUTIONS

**Author *:** Conceptualization, Data Collection, Methodology, Writing - Original Draft, Resources, and Software.

**Author **:** Approval, Formal analysis, and Supervision.

**Author ***:** Conceptualization, Methodology, Data Curation, Writing - Review & Editing.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This was an observational study, and ethical approval was obtained from the Office of the Ethics Committee, SMS Medical College and Attached Hospitals, Jaipur (Reference No: 731/MC/EC/2023).

## COMPETING INTEREST

The authors declare that they have no competing interests.

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## Original Article

# Comparative Analysis of Tanner Whitehouse-2 (TW2) and Tanner Whitehouse-3 (TW3) Methods for Forensic Skeletal Age Estimation in Adolescents (14–18 Years) in a Tertiary Care Hospital

**Mahesh Kumar Meena*, Mukesh Mittal**, Sumanta Dutta***, Priyanka Sharma****, Anupam Rajoria*****


## ABSTRACT

**Background:** Determining chronological age around the legal threshold of 18 years is a critical component of forensic evaluation, particularly in jurisdictions governed by juvenile justice and child protection laws. Skeletal age estimation using hand–wrist radiographs remains a widely accepted approach. The Tanner–Whitehouse method has evolved from its second edition (TW2) to the updated third edition (TW3) to accommodate changing growth patterns. This study compares the performance of these two methods in an Indian adolescent population.

**Methods:** A hospital-based cross-sectional study was conducted on 100 healthy adolescents (50 males and 50 females) aged 14–18 years. Chronological age was verified using official records. Standardized radiographs of the left hand and wrist were assessed using the Radius–Ulna–Short bones (RUS) scoring system under both TW2 and TW3 protocols. Estimated skeletal ages were compared with chronological age, and statistical measures including mean deviation, correlation coefficient, and standard error were calculated.

**Results:** Both TW2 and TW3 methods demonstrated strong positive correlation with chronological age. However, TW2 consistently produced higher age estimates, with mean overestimations of +0.73 years in males and +0.48 years in females. In contrast, TW3 showed lower deviations (+0.22 years in males and +0.14 years in females), along with improved correlation and reduced standard error.

**Conclusion:** The TW3 method provides greater accuracy and reliability for skeletal age estimation in adolescents from North India. The systematic overestimation observed with TW2 may have important medico-legal implications, particularly in age-disputed cases. Adoption of TW3 is recommended for forensic practice in this population.


**Keywords:** skeletal age, forensic age estimation, Tanner–Whitehouse, adolescents, radiography, chronological age.

## INTRODUCTION

In forensic practice, determining whether an individual has reached the legal age of majority (18 years) is paramount for cases under the Protection of Children from Sexual Offences (POCSO) Act and juvenile justice frameworks. Skeletal age assessment (SAA) of the hand and wrist is the gold standard for this developmental window. The Tanner-Whitehouse (TW) method, which uses a point-scoring system for specific ossification centers , has undergone revisions from TW2 to TW3 to account for secular trends in human growth. The Tanner-Whitehouse (TW) protocol evaluates skeletal development by examining distinct ossification centers within the wrist and hand. This assessment is categorized into two primary systems: the RUS component, which focuses on the radius, ulna, and specific short bones (metacarpals and phalanges), and the Carpal component, which inventories the carpal bones while excluding the pisiform from the final analysis. The individual bones are matched to a series of written criteria describing eight or nine standard stages, labelled A to I, through which each bone passes in its progression to maturity. Each stage is defined by up to three criteria and is assigned a specific score. The sum of these scores results in a skeletal maturity score (SMS) that can be transformed into skeletal age. This study aims to validate these methods for the specific demographic of Jaipur, Rajasthan, providing evidence-based tools for medico-legal experts.

## MATERIAL AND METHODS

One hundred participants (50 males, 50 females) aged 14.0 to 17.99 years were recruited from the local population of Jaipur. Chronological age (CA) was verified via official birth certificates. Digital PA radiographs of the left hand-wrist were obtained. Each radiograph was scored according to the maturity stages (A-I) for the Radius, Ulna, and Short bones (RUS) using both the TW2 and TW3 protocols.


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## RESULTS

Table 1: Mean Chronological Age vs. Skeletal Age (TW2 & TW3)

| Gender | Mean CA (Years) | Mean SA (TW2) |
|---|---|---|
| **Male (n=50)** | 16.12 | 16.85 |
| **Female (n=50)** | 15.94 | 16.42 |

Table 2: Mean Skeletal Age Deviation (SAD) Comparison

| Method | Male Deviation (Years) | Female Deviation (Years) |
|---|---|---|
| **TW2 Method** | +0.73 | +0.48 |
| **TW3 Method** | +0.22 | +0.14 |

Table 3: Correlation Analysis ($R^2$ Values)

| Statistical Metric | TW2 Method | TW3 Method |
|---|---|---|
| **Coefficient of Correlation (R)** | 0.88 | 0.92 |
| **Standard Error of Estimate** | 0.64 | 0.38 |

### Skeletal Age Deviation (SAD) Analysis

The statistical analysis revealed that the TW2 method significantly overestimates age compared to the TW3 method. The Mean SAD for the TW3 method (+0.14 to +0.22) was substantially lower than that of TW2 (+0.48 to +0.73). Correlation analysis showed a high coefficient for both, though TW3 demonstrated a higher $R^2$ value (0.92) and a lower Standard Error of Estimate (0.38) than TW2 (0.88 and 0.64 respectively).

## DISCUSSION

Accurate age estimation in adolescents approaching the legal threshold of 18 years is a fundamental requirement in forensic practice, particularly in India where legal outcomes under statutes such as the Protection of Children from Sexual Offences (POCSO) Act and juvenile justice frameworks are strictly age-dependent. Even minimal discrepancies between estimated and true age may significantly alter judicial decisions. Skeletal age assessment (SAA) using hand–wrist radiographs continues to be one of the most dependable biological indicators during adolescence due to its reproducibility and well-established maturation sequence.

The findings of the present study demonstrate that both TW2 and TW3 methods exhibit a strong positive correlation with chronological age (CA), supporting their continued relevance in skeletal maturity assessment. However, TW2 consistently showed a tendency to overestimate age compared to TW3. This pattern has been widely reported in earlier studies and is largely attributed to the historical context in which TW2 standards were developed. The TW2 method is based on mid-20th century reference populations and does not adequately account for secular trends in growth and development.

Secular acceleration, driven by improved nutrition, healthcare, and overall socioeconomic advancement, has led to earlier skeletal maturation in contemporary populations. This trend has been documented across multiple geographic regions, including European and Asian populations, indicating a global shift in growth patterns. As a consequence, methods such as TW2 tend to systematically overestimate age when applied to present-day adolescents. The degree of overestimation observed in our study (mean skeletal age deviation of +0.73 years in males and +0.48 years in females) is consistent with previously published literature.

In contrast, the TW3 method was designed to address these limitations by incorporating updated reference data and revised scoring criteria that better reflect modern growth dynamics. The significantly lower skeletal age deviation observed with TW3 in this study (+0.22 years in males and +0.14 years in females) highlights its improved accuracy. Furthermore, TW3 demonstrated a higher correlation coefficient and a lower standard error of estimate, findings that are in agreement with other validation studies.

From a medico-legal perspective, the implications of such differences are substantial. Overestimation of age may result in a minor being incorrectly classified as an adult, thereby exposing them to more severe legal consequences. This issue, often described as “judicial over-aging,” raises important ethical and legal concerns, particularly in cases where age determination is contested. The inherent bias of TW2 towards overestimation makes it less suitable for forensic use in modern populations, where accuracy and fairness are paramount.

Population-specific variability is another critical factor influencing skeletal maturation. Genetic background, environmental conditions, and nutritional status all contribute to differences in growth patterns across populations. Studies conducted in Indian cohorts have demonstrated variations when compared to Western standards, emphasizing the importance of regional validation. The present study adds to this body of evidence by providing data specific to adolescents from Jaipur, Rajasthan, thereby supporting the applicability of TW3 in this regional context.

Despite its strengths, including a balanced sample size and standardized radiographic methodology, this study has certain limitations. The relatively modest sample size may not fully capture the diversity of the broader population, and the cross-sectional design limits the ability to observe longitudinal growth trends. Future studies should focus on larger, multicentric datasets and explore the development

of region-specific correction factors or regression models to further enhance accuracy.

Recent advancements in forensic age estimation, including automated bone age assessment systems and the integration of multiple biological markers such as dental and clavicular ossification, offer promising avenues for improving precision. However, these methods require further validation before widespread adoption in routine forensic practice. At present, radiographic assessment using the TW3 method remains a practical, reliable, and legally acceptable standard.

This study reinforces that while both TW2 and TW3 methods are useful for skeletal age estimation, TW3 provides superior accuracy and reduced bias in contemporary adolescent populations. Given the significant medico-legal implications of age estimation, particularly in borderline cases, the adoption of TW3 is strongly recommended to ensure fairness, reliability, and scientific validity in forensic evaluations.

## CONCLUSION

The findings of this research emphasize that the choice of skeletal age estimation methodology has significant legal and ethical ramifications. For the adolescent population in Jaipur, the Tanner Whitehouse-3 (TW3) method demonstrated superior reliability and precision compared to the older TW2 version. TW2's tendency to overestimate age could inadvertently lead to a juvenile being processed through the adult justice system, a critical error in forensic practice.

## ABBREVIATIONS

POCSO: The Protection of Children from Sexual Offences
S.M.S: Skeletal Maturity Score
TW: Tanner-Whitehouse Method
CA: Chronological Age
SA: Skeletal Age
RUS: Radius, Ulna and Short Bones/ radio, ulna and selected metacarpals and phalanges
SAA: Skeletal age assessment
SAD: Skeletal Age Deviation

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## AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are not made publicly available due to concerns of patient privacy and are available from the corresponding author upon reasonable request.

## AUTHORS' CONTRIBUTIONS

**Author ***: participated in data collection, writing and follow up of the patient.

**Author ****: participated in the supervision, writing and editing.

**Author *****: conceptualization, methodology, supervision and validation.

**Author ******: participated in supervision and reviewing.

**Author *****:** participated in manuscript drafting.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study has been conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from the patient for the publication of their clinical information and any accompanying images. Confidentiality has been maintained throughout the manuscript, with all identifiers removed to protect the patient's privacy.

## COMPETING INTEREST

The authors declare that they have no competing interests.

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## Original Article

# Prevalence and Pattern of Psychoactive Substance Use among Undergraduate Medical Students in a Public Medical College of North India a Cross-Sectional Study

**Kritika Jain*, Monika Rathore**, Govardhan Meena***, Rohan Garg****, Dharmesh Sharma*****, Muskan Jain******


## ABSTRACT

**Background:** Substance use among medical students is an emerging public health concern due to academic stress, peer influence, and easy accessibility of psychoactive substances. Use of alcohol, tobacco, cannabis, and prescription drugs among medical trainees may affect academic performance, professional conduct, and future patient care practices.

**Objectives:** To estimate the prevalence and pattern of psychoactive substance use among undergraduate MBBS students in a public medical college of North India.

**Methods:** An institute-based cross-sectional descriptive study was conducted among 750 undergraduate MBBS students over one month using universal sampling. Data were collected through a pretested, structured, self-administered questionnaire assessing type of substance used, age at initiation, frequency, reasons for use, expenditure, willingness to quit, and help-seeking behaviour. Data were analysed using descriptive statistics and Chi-square test, with $p < 0.05$ considered statistically significant.

**Results:** Prevalence of substance use was 27.46%, with significantly higher use among males (74.27%). Alcohol was the most common substance (86.89%), followed by tobacco (47.57%) and cannabis (25.24%). Prescription drug use was reported by 21.84%. Experimentation and peer influence were common reasons for initiation, while celebration and desire to feel high were major reasons for continued use.

**Conclusion:** Substance use is common among medical students, indicating the need for counselling, stress management, and preventive interventions.


**Keywords:** Substance-Related Disorders, Students, Medical; Prevalence, Psychotropic Drugs, Alcohol Drinking, tobacco, Cross-Sectional Studies.

## INTRODUCTION

Substance abuse, defined as the harmful or hazardous use of psychoactive substances including alcohol, tobacco, cannabis, opioids, stimulants, and misuse of prescription medications, represents a major public health challenge globally. Approximately 296 million people aged 15–64 years used psychoactive substances worldwide in 2021, of whom nearly 39.5 million suffered from drug use disorders (United Nations Office on Drugs and Crime UNODC). It is estimated that substance use contributes nearly 0.6 million deaths annually to the global morbidity (WHO). National surveys of India indicate that alcohol, tobacco, and cannabis remain the most commonly used substances, reflecting a growing burden among young adults.

College students are high-risk population due to developmental transitions, psychosocial vulnerability, increased autonomy, and exposure to new peer environments. Medical education is characterized by intense academic pressure, competitive learning environments, irregular sleep schedules, emotional stress, and early exposure to clinical responsibility. These stressors may predispose medical students to maladaptive coping behaviours including psychoactive substance use. The prevalence of substance use among medical students of India ranging from 32.5% to 81.2%, highlighting considerable variability across settings. Recent cross-sectional studies have reported lifetime substance use prevalence ranging from 36% to 46% among medical students, with alcohol being the most commonly used substance followed by tobacco and cannabis. Substance use has been associated with academic stress, peer influence, curiosity, and perceived improvement in concentration or sleep.

Substance abuse among medical students is of particular concern as it may impair cognition, academic performance, professionalism, and clinical decision-making. Emerging evidence suggests a shift towards increased use of cannabis, sedatives, stimulants, and prescription medications in addition to alcohol. Cannabis use has been associated with impaired memory, reduced attention, and poorer academic outcomes. Medical students are future physicians whose personal health behaviours influence patient counselling, practices and public health advocacy.

Despite increasing recognition of this issue, limited recent evidence is available regarding the prevalence and pattern of substance abuse among undergraduate MBBS

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students in Rajasthan. Context-specific data are essential to inform targeted preventive strategies, early screening mechanisms, and student wellness programmes. Therefore, the present study aims to estimate the prevalence and pattern of substance abuse among undergraduate MBBS students in a public medical college in Jaipur.

## MATERIALS AND METHODS

### Study Design and Setting

An institute-based cross-sectional descriptive study was conducted among undergraduate medical students of SMS Medical College, a premier government medical institution in North India. Cross-sectional design is commonly employed in epidemiological studies assessing prevalence and patterns of substance use among medical students. The study was conducted over a period of one month.

### Study Population and Eligibility Criteria

Undergraduate MBBS students enrolled in 2nd, 3rd and final year of the MBBS course during the study period. Students who declined participation or submitted incomplete responses on google form were excluded from analysis.

### Sample Size and Sampling Strategy

A total of 750 undergraduate MBBS students constituted the sampling frame. Universal sampling was adopted, wherein all eligible students from the selected batches were invited to participate in the study. Universal sampling has been utilized in similar institutional studies to improve representativeness and reduce sampling error.

### Study Variables

The primary outcome variable was the prevalence (proportion) of substance use among undergraduate medical students. Secondary outcome variables included pattern of substance use, type of substance consumed (alcohol, tobacco, cannabis, sedatives, stimulants, opioids and others), age of initiation, frequency and quantity of consumption, reasons for use, monthly expenditure, willingness to quit, and preferred source of help for cessation. Covariates included age, sex and academic year.

### Study Tool and Data Collection

Data were collected using a structured, self-administered questionnaire developed after review of relevant literature assessing substance use among medical students. The google form questionnaire consisted of 10 closed-ended items covering type of substance used, age at initiation, frequency, quantity, reasons for use (peer pressure, stress, curiosity, recreational purpose), monthly expenditure, willingness to quit, and help-seeking preferences.

The tool was pretested among 20 undergraduate medical students outside the study sample to assess clarity, feasibility, and comprehension. Content validity was established through expert review by three faculty members (two from Community Medicine and one from Psychiatry). Necessary modifications were made prior to final data collection. Self-administered anonymous questionnaires were used to minimize reporting bias and improve validity in studies assessing sensitive behaviours such as substance use.

### Bias

Anonymity and confidentiality were ensured to minimize social desirability bias and under-reporting. Standardized instructions were provided to reduce interviewer bias.

### Statistical Analysis

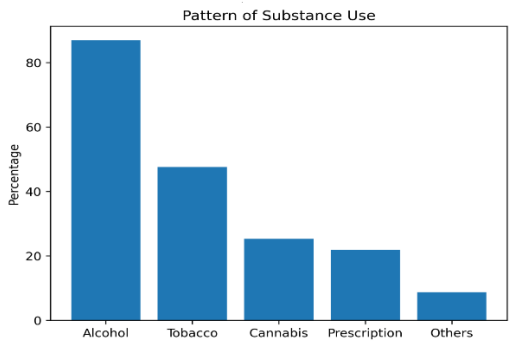
Data were entered in Microsoft Excel and analysed using statistical software. Continuous variables were summarized using mean and standard deviation, while categorical variables were expressed as proportions and percentages. Difference between proportions was assessed using Chi-square test or Fisher's exact test as appropriate. Comparison of means between two groups was performed using Student's t-test, and comparison among more than two groups was performed using one-way ANOVA. The level of statistical significance was set at $p < 0.05$ with 95% confidence interval. Statistical methods similar to previous cross-sectional studies assessing substance use among medical students were applied.

## RESULTS

### Prevalence of Substance Use

**There were 206** out of 750 undergraduate MBBS students, who **consumed one or more psychoactive substances,** giving an overall **prevalence of 27.46%.**

**alcohol (86.89%)** was the most commonly consumed substance, followed by **tobacco (47.57%), cannabis (25.24%),** and **medical/prescription drugs (21.84%).** Use of other substances was reported by **8.73%** of participants. The findings suggest a rising trend of prescription drug misuse among medical students, possibly related to ease of accessibility.



## Association of Substance Use with Socio-Demographic Variables

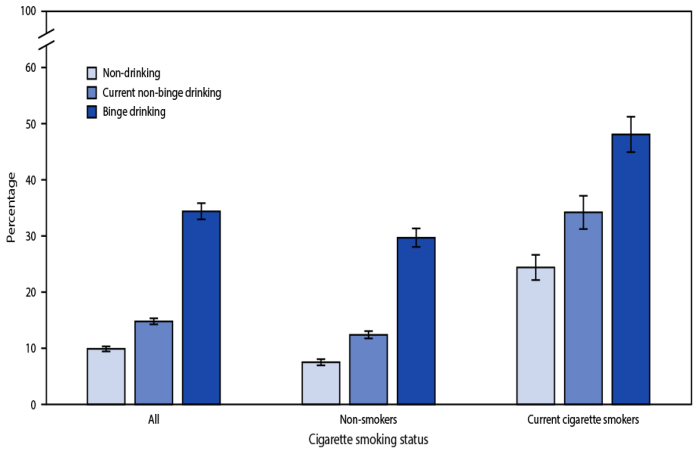
Substance use varied significantly across age groups ($\chi^2$ = 26.78, df = 3, **p < 0.001**), The highest was in age group of **≥24 years (50.0%),** followed by **22–23 years (30.18%), 20–21 years (24.37%),** and **18–19 years (10.34%).**

Gender was also significantly associated with substance use with male preponderance **74.27% (153/206)** males vs **25.73% (53/206)** females ($\chi^2$ = 12.37, df = 1, **p < 0.001**).

Table 1. Association with socio-demographic variables

| Study variable | Substance Use | | Total | Level of Significance |
|---|---|---|---|---|
| | Yes | No | | |
| AGE(n=750) | | | | |
| 18-19 | 6 | 52 | 58 | $X^2$ value= 26.78 Df= 3 p < 0.001 Significant |
| 20-21 | 87 | 270 | 357 | |
| 22-23 | 83 | 192 | 275 | |
| ≥24 | 30 | 30 | 60 | |
| GENDER(n=750) | | | | |
| Male | 153 | 329 | 482 | $X^2$ value= 12.73 Df= 1 p < 0.001 Significant |
| Female | 53 | 215 | 268 | |

## Pattern of Substances Used



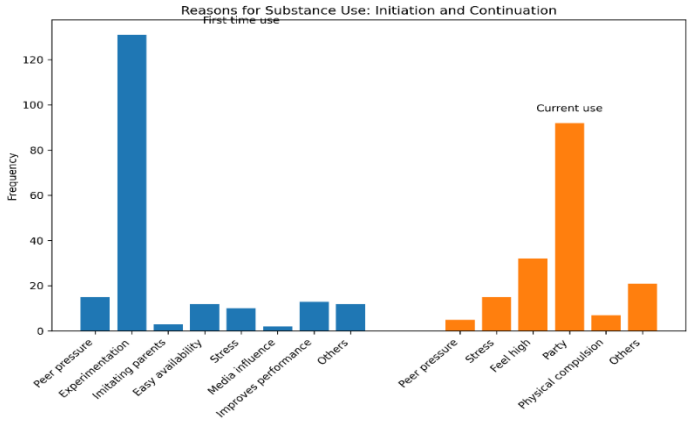

| Study variables | Number of subjects (n=206) | Study variables | Number of subjects (n=206) |
|---|---|---|---|
| **1. Age of starting**: | | **2. Frequency:** | |
| • <10 | 15(7.28%) | • During weekdays | 30(14.56%) |
| • 10-13 | 5(2.42%) | • On weekends | 13(6.31%) |
| • 14-19 | 31(15.53%) | • Once in a month | 39(18.93%) |
| • >19 | 147(71.35%) | • Once in six months | 79(38.34%) |
| **3. Place of first trial**: | | **4. Monthly expenditure**: | |
| • School/ hostel | 17(8.25%) | • Less than 1000rs. | 85(41.26%) |
| • College /hostel | 137(66.50%) | • 1000-5000rs. | 16(7.76%) |
| • Home | 25(12.13%) | • >5000rs. | 15(7.28%) |
| • Other | 13(6.31%) | | |
| **5.First time source**: | | | |
| • Shop | 27(13.10%) | | |
| • Friends | 138(66.99%) | | |
| • Dealer | 12(5.82%) | | |
| • Parents | 14(6.79%) | | |
| • Other | 8(3.38%) | | |

## Initiation of Substance Use

Majority of participants reported initiating substance use **after 19 years of age (71.35%)**, followed by **14–19 years (15.53%)**, while early initiation before 13 years was relatively less common **(9.70%)**. The most common setting for first trial was **college/hostel (66.50%)**, followed by **home (12.13%), school/hostel (8.25%)**, and other places (6.31%). Friends were the predominant source of first exposure **(66.99%)**, followed by shops **(13.10%)**, parents **(6.79%)**, and dealers **(5.82%)**.

## Frequency and Expenditure Pattern

Regarding frequency of consumption, 38.34% reported use once in six months, 18.93% once monthly, 14.56% during weekdays, and 6.31% during weekends. Monthly expenditure on substances was < ₹1000 in 41.26%, ₹1000–5000 in 7.76%, and > ₹5000 in 7.28% of users.




| REASON FOR SUBSTANCE ABUSE (n=206) | |
|---|---|
| **FOR FIRST TIME:** | **Frequency (%)** |
| • Experimentation | 131 (63.59%) |
| • Peer pressure | 15 (7.28%) |
| • Imitating parents | 3 (1.4%) |
| • Easy availability | 12 (5.82%) |
| • Stress | 10 (4.85%) |
| • Influence of media | 2 (0.97%) |
| • Improves performance | 13 (6.31%) |
| • Others | 12 (5.82%) |
| **Continuation of substance use:** | |
| • Peer pressure | 5 (2.42%) |
| • Stress | 15 (7.28%) |
| • To feel high | 32 (15.53%) |
| • Celebration/parties | 92 (44.66%) |
| • Physical compulsion | 7 (3.39%) |
| • Others | 21 (10.19%) |

### Reasons for Initiation and Continuation

Experimentation was the most common reason for first-time substance use **(63.59%),** followed by peer pressure **(7.28%),** perceived performance improvement **(6.31%),** easy availability **(5.82%),** and stress **(4.85%).**

For continued use, the most common reasons were **celebrations/parties (44.66%), desire to feel high (15.53%), stress (7.28%),** and **peer pressure (2.42%),** while **3.39%** reported physical compulsion.

### Willingness to Quit and Help-Seeking Behaviour

Approximately **50% of substance users reported willingness to quit.** Among those willing to discuss substance-related concerns, **66.25% preferred informal support,** most commonly **friends (40.49%)** and **siblings (7.97%),** whereas relatively fewer participants preferred seeking professional help or discussing with parents.

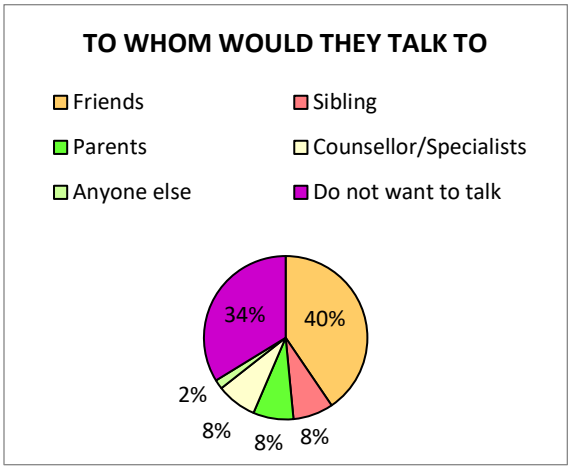
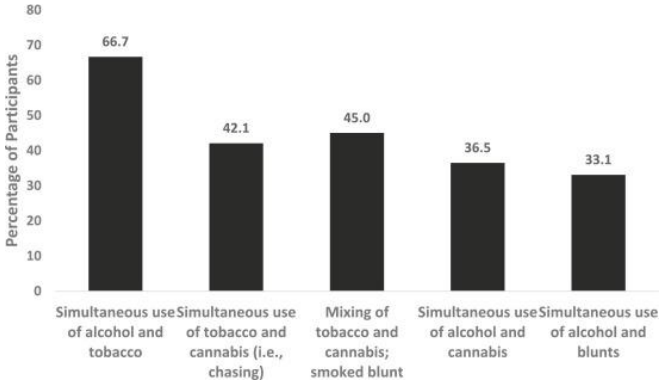



Figure 1: Type of substances used among medical students




## DISCUSSION

The present study found that **27.46%** of undergraduate MBBS students reported use of one or more psychoactive substances, indicating that substance use remains a significant concern among future healthcare professionals. Comparable prevalence has been reported in Indian studies among medical students, ranging from 23% to 38%. Sharma et al. reported prevalence of 32.6%, while Bant et al. observed prevalence of 30.1%, demonstrating similar magnitude across institutional settings. Differences in prevalence may be explained by variation in study design, sociocultural context, and willingness of participants to disclose substance use.

Substance use was significantly associated with increasing age, with higher prevalence among senior students. Similar findings have been reported in Indian studies where substance use increased with academic progression, possibly due to increased academic workload, examination stress, hostel residence, and greater autonomy. Male predominance observed in the present study is consistent with previous literature, reflecting sociocultural acceptance and greater opportunity for substance use among males.

Alcohol was the most commonly consumed substance, followed by tobacco and cannabis, consistent with national data identifying alcohol as the predominant psychoactive substance among young adults in India. Cannabis use observed in the present study aligns with recent literature suggesting increasing experimentation among college students. Notably, more than one-fifth of participants reported use of prescription drugs, highlighting an emerging concern regarding accessibility of medications among medical trainees. Similar patterns of non-medical use of sedatives and stimulants have been reported in healthcare students.

Experimentation and peer influence were the leading reasons for initiation, while celebration and recreational use were common reasons for continuation. Similar determinants have been reported in previous studies among university students. Although nearly half of the participants expressed willingness to quit, preference for informal support indicates stigma associated with seeking professional help. Strengthening confidential counselling services, peer-support mechanisms, and stress management programmes may help reduce substance use among medical students.

## CONCLUSION

The present study demonstrates that substance use is prevalent among undergraduate MBBS students, with more than one-fourth of students reporting consumption of at least one psychoactive substance. Alcohol was the most commonly used substance, followed by tobacco and cannabis, while a considerable proportion reported misuse of prescription drugs, indicating increasing accessibility within medical settings. Substance use was significantly associated with increasing age and male gender. Experimentation and peer influence were the major factors for initiation, whereas recreational use during celebrations was a common reason for continuation. These findings highlight the need for early preventive interventions to

promote healthy coping strategies and ensure wellbeing of future healthcare professionals.

## RECOMMENDATIONS

Medical institutions should implement comprehensive strategies to address substance use among undergraduate students. Regular awareness programmes focusing on harmful effects of psychoactive substances and responsible behaviour should be incorporated into the medical curriculum. Periodic screening for substance use and psychological stress may help in early identification of at-risk students. Establishment of confidential counselling services, mentorship systems, and peer-support groups can encourage help-seeking behaviour and reduce stigma. Stress management interventions such as mindfulness training, recreational activities, and academic counselling may promote healthy coping mechanisms. Strict regulation of access to prescription medications within institutional settings is also recommended. Multi-sectoral collaboration involving faculty, mental health professionals, and student bodies is essential for creating a supportive environment that discourages substance use and promotes overall student wellbeing.

## ABBREVIATIONS

MBBS – Bachelor of Medicine, Bachelor of Surgery
WHO – World Health Organization
UNODC – United Nations Office on Drugs and Crime
CI – Confidence Interval
SD – Standard Deviation
ANOVA – Analysis of Variance
$\chi^2$ – Chi-square test

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## AVAILABILITY OF DATA AND MATERIALS

Data will be available by emailing kritikatie@gmail.com

## AUTHORS' CONTRIBUTIONS

**Author ***: participated in the investigation, conceptualization, methodology, resources, supervision, validation, writing, reviewing, and editing.

**Author ****: participated in the investigation, conceptualization, writing, review, data collection, and editing.

**Author *****: corresponding author participated in writing, reviewing, and editing.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

## COMPETING INTEREST

The authors declare that they have no competing interests.

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## Review Article

# Managing Dyslipidemia in 2026: Key Updates from the ACC/AHA Guideline for Clinical Practice

**Nivedita Gupta*, Jitendra Kumar Gupta**, Amitabh Dube***, Monica Jain****, Dhruva Sharma*****, Shivankan Kakkar******


## ABSTRACT

**Background:** The 2026 ACC /AHA /AACVPR /ABC /ACPM /ADA /AGS /APhA /ASPC /NLA /PCNA Guideline on the Management of Dyslipidemia represents the most comprehensive update to lipid management guidance since the 2018 Blood Cholesterol Guideline. Released in 2026 and published in Circulation, this collaborative multisociety document retires and replaces its predecessor and reflects major advances in cardiovascular risk assessment, lipoprotein biology, and pharmacotherapy.

**Key Updates:** The guideline introduces the AHA PREVENT™ equations as the new standard for 10- and 30-year ASCVD risk estimation, replacing the older Pooled Cohort Equations (PCE). LDL-C and non-HDL-C numerical treatment goals are formally reinstated alongside percentage-reduction targets. Lipoprotein(a) [Lp(a)] measurement is now recommended at least once in all adults. Coronary artery calcium (CAC) scoring receives expanded guidance for risk reclassification and treatment intensity decisions. Novel pharmacological agents, including olezarsen for familial chylomicronemia syndrome and bempedoic acid supported by the CLEAR OUTCOMES trial, are integrated into the treatment framework. Special population recommendations are substantially expanded, including new COR 1 guidance for statin use in people living with HIV.

**Clinical Relevance:** This update shifts dyslipidemia management toward earlier intervention, more precise risk stratification, and a broader pharmacological armamentarium. Clinicians across primary care, cardiology, endocrinology, and preventive medicine disciplines must be familiar with these practice-changing recommendations to optimise cardiovascular risk reduction in their patient populations.


**Keywords:** dyslipidemia; LDL-C lowering; PREVENT equations; lipoprotein(a); coronary artery calcium; statin therapy; ASCVD prevention; bempedoic acid; PCSK9 inhibitors.

## INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality globally, with atherosclerotic cardiovascular disease (ASCVD) accounting for the majority of deaths and a substantial burden of disability. Dyslipidemia—characterised by elevated low-density lipoprotein cholesterol (LDL-C), hypertriglyceridaemia, reduced high-density lipoprotein cholesterol (HDL-C), and elevated lipoprotein(a) [Lp(a)]—is a primary, modifiable risk factor in this pathway. The causal relationship between atherogenic lipoproteins and ASCVD is established with high certainty through decades of epidemiological data, Mendelian randomisation studies, and randomised controlled trials (RCTs) of lipid-lowering therapies (LLTs).

The 2026 ACC/AHA guideline represents a watershed moment in the evolution of lipid management guidance.1 It retires and replaces the 2018 Blood Cholesterol Guideline and introduces substantive changes across risk assessment, treatment thresholds, lipoprotein targets, and pharmacotherapy. It is also significantly retitled from the 'Guideline on the Management of Blood Cholesterol' to the 'Guideline on the Management of Dyslipidemias'—reflecting the evolving understanding that ASCVD risk extends beyond LDL particles to encompass triglyceride-rich lipoprotein remnants and Lp(a).

For practising clinicians, the sheer scope and complexity of the updated guidance may be challenging to navigate. This article distils the most clinically impactful updates, organised thematically, and provides practical commentary to facilitate their translation into daily patient care.

## A NEW ERA OF RISK ASSESSMENT: THE PREVENT™ EQUATIONS

### Replacing the Pooled Cohort Equations

One of the most consequential changes in the 2026 guideline is the formal replacement of the Pooled Cohort Equations (PCE) with the American Heart Association's

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PREVENT™ (Predicting Risk of Cardiovascular Disease EVENTs) equations for 10- and 30-year ASCVD risk estimation in adults aged 30 to 79 years without established ASCVD or subclinical atherosclerosis.

The PCE were derived from approximately 25,000 individuals from older birth cohorts and were widely recognised to **overestimate ASCVD risk**—often by 20–40%—in contemporary populations. The PREVENT equations were derived from over 3.3 million contemporary US adults and validated in a separate cohort of similar size, representing a substantially more accurate and contemporarily calibrated tool. In general, PREVENT risk estimates are 40–50% lower than PCE estimates for the same risk factor profile. Importantly, race and ethnicity are not included as predictor variables in PREVENT, as they did not add predictive value when other clinical variables were accounted for.

### The 'CPR' Framework and New Risk Thresholds

The guideline introduces the 'CPR' model as a practical framework for clinicians: Calculate 10-year ASCVD risk using PREVENT; Personalise the estimated risk by considering factors not captured in PREVENT (risk enhancers); and possibly Reclassify with selective use of coronary artery calcium (CAC) scoring and reassessment of treatment recommendations.

Given the improved accuracy of PREVENT, the threshold for initiating the benefit-risk discussion regarding LLT is now set at a 10-year PREVENT-ASCVD risk of ≥3% (previously ≥5% using PCE). Risk categories are defined as: low (<3%), borderline (3% to <5%), intermediate (5% to <10%), and high (≥10%). A net clinical benefit from moderate-intensity statin therapy has been demonstrated at a 10-year event rate as low as 3%, supporting this lower threshold.

Risk enhancers—including elevated Lp(a) (≥125 nmol/L or ≥50 mg/dL), persistently elevated triglycerides (≥150 mg/dL fasting), chronic inflammatory diseases, cardiovascular-kidney-metabolic (CKM) syndrome, premature family history of ASCVD, and reproductive risk markers (e.g., preeclampsia, gestational diabetes, early menopause)—should be considered in the benefit-risk discussion, particularly for borderline-risk individuals. Their presence can support initiation or intensification of LLT even when calculated risk alone may not reach a decision threshold.

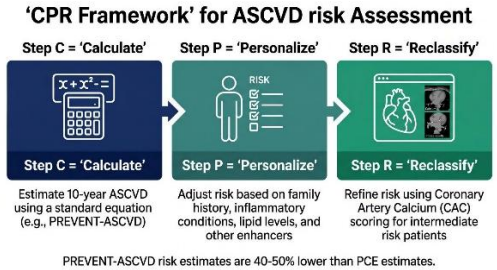


Figure 1. The CPR Framework for Cardiovascular Risk Evaluation

## RETURN OF LDL-C TREATMENT GOALS

A defining feature of the 2026 guideline is the reinstatement of absolute LDL-C and non-HDL-C treatment goals alongside percentage-reduction targets. This represents a significant departure from the 2018 guideline, which emphasised percentage reduction over absolute targets. The rationale is well-supported by evidence demonstrating that lower achieved LDL-C levels—independent of percentage reduction—correlate with better cardiovascular outcomes.

### Goal-Based Treatment Targets by Risk Group

Treatment goals are now stratified by patient risk group and clinical context. For **primary prevention** in borderline to intermediate risk (3% to <10%), statin therapy should achieve ≥30–49% LDL-C reduction with a goal of LDL-C <100 mg/dL and non-HDL-C <130 mg/dL. For **high-risk primary prevention** (≥10%), high-intensity statin targeting LDL-C <70 mg/dL and non-HDL-C <100 mg/dL is recommended. In **secondary prevention for very high-risk ASCVD**, the goal is LDL-C <55 mg/dL and non-HDL-C <85 mg/dL—reinforcing the 'lower is better' principle supported by FOURIER, ODYSSEY OUTCOMES, and IMPROVE-IT.

### The Role of ApoB as a Complementary Target

Apolipoprotein B (apoB) is now formally endorsed as a complementary measurement to guide therapeutic intensification, particularly after LDL-C and non-HDL-C goals are achieved. Unlike LDL-C, which reflects cholesterol mass within LDL particles, apoB directly quantifies the number of atherogenic lipoprotein particles (with one apoB per LDL, VLDL, and Lp(a) particle). In patients with CKM syndrome, diabetes, or elevated triglycerides, LDL-C may be at goal while apoB remains elevated—a state of 'discordance' representing residual atherogenic particle burden that may warrant further treatment.

Optional apoB goals are now specified for each risk group: <90 mg/dL for primary prevention (borderline to intermediate risk), <70 mg/dL for high-risk primary prevention and most secondary prevention patients, and <55 mg/dL for very high-risk secondary prevention patients, including those with CKD.

Table 1. Lipoprotein Treatment Goals by Patient Group (2026 ACC/AHA Guideline)

| Patient Group | LDL-C Goal | Non-HDL-C Goal | % LDL-C Reduction | Optional apoB |
|---|---|---|---|---|
| **Primary Prevention** | | | | |

| Patient Group | LDL-C Goal | Non-HDL-C Goal | % LDL-C Reduction | Optional apoB |
|---|---|---|---|---|
| Borderline–Intermediate Risk (3–10%) | **<100 mg/dL** | **<130 mg/dL** | ≥30–49% | <90 mg/dL |
| High Risk (≥10%) | **<70 mg/dL** | **<100 mg/dL** | ≥50% | <70 mg/dL |
| **Secondary Prevention (Clinical ASCVD)** | | | | |
| Not at Very High Risk | **<70 mg/dL** | **<100 mg/dL** | ≥50% | <70 mg/dL |
| Very High Risk* | **<55 mg/dL** | **<85 mg/dL** | ≥50% | <55 mg/dL |
| **Subclinical Atherosclerosis (CAC Score)** | | | | |
| CAC 1–99 AU (<75th %ile) | **<100 mg/dL** | **<130 mg/dL** | ≥30–49% | <100 mg/dL |
| CAC 100–999 AU or ≥75th %ile | **<70 mg/dL** | **<100 mg/dL** | ≥50% | <70 mg/dL |
| CAC ≥1000 AU | **<55 mg/dL** | **<85 mg/dL** | ≥50% | <55 mg/dL |

*Very High Risk = ≥2 major ASCVD events OR 1 major event + ≥2 high-risk conditions (age >65y, revascularisation, smoking, diabetes, HF, HTN, LDL-C >100 on max statin+ezetimibe). AU: Agatston units; CAC: coronary artery calcium.

## CORONARY ARTERY CALCIUM SCORING: EXPANDED ROLE IN RISK STRATIFICATION

CAC scoring is given a substantially expanded role in the 2026 guideline, with new COR 1 recommendations for its use and new treatment goal specifications tied to CAC scores. CAC testing using non-contrast gated cardiac CT is recommended for risk reclassification in men ≥40 years and women ≥45 years in whom the decision about initiating LLT remains uncertain after risk calculation and personalisation.

### CAC Score and Treatment Decisions

A CAC score of **zero** (CAC=0) strongly predicts a low 10-year ASCVD risk and is associated with very low observed event rates. In adults at intermediate or borderline risk with CAC=0 and no high-risk conditions (FH, severe hypercholesterolaemia ≥190 mg/dL, diabetes and age >40 years, current smoking, or strong premature family history of ASCVD), it is reasonable to defer LLT and reassess with repeat CAC testing in 3–7 years. Importantly, CAC=0 does **not** justify withholding statin therapy in patients with FH or severe hypercholesterolaemia.

Conversely, if CAC is >**0,** initiation of LLT is recommended (COR 1). A CAC score ≥100 AU or ≥75th standardised percentile (adjusted for age, sex, and race) corresponds to high risk—with observed 10-year event rates comparable to secondary prevention cohorts—and warrants high-intensity LLT targeting LDL-C <70 mg/dL. For very extensive CAC (≥1000 AU), the treatment target aligns with secondary prevention goals: LDL-C <55 mg/dL and non-HDL-C <85 mg/dL (COR 1).

### Incidental CAC on Non-cardiac CT Scans

An important new COR 1 recommendation covers incidental CAC identified on non-cardiac CT scans (e.g., low-dose CT for lung cancer screening, routine abdominal CT). When moderate-to-severe coronary calcification is detected by visual estimation or validated AI-based algorithms, this should be factored into LLT decision-making. Clinical interventions following notification of incidental CAC results have been shown to substantially increase appropriate statin prescribing.

## PHARMACOTHERAPY: AN EXPANDING TOOLKIT

### Statins Remain the Foundation

High-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) remains the first-line pharmacological intervention for LDL-C lowering and ASCVD risk reduction across all risk categories. Statins are categorised by expected LDL-C reduction: high-intensity (≥50%), moderate-intensity (30–49%), and low-intensity (<30%). The 2026 guideline reinforces that the magnitude of LDL-C reduction, not the choice of statin per se, determines cardiovascular benefit.

### Nonstatin Therapies: Evolving Evidence and Indications

Ezetimibe provides an incremental 25% LDL-C reduction when added to statin therapy and has demonstrated cardiovascular benefit in high-risk secondary prevention (IMPROVE-IT). It is now the preferred first add-on to statin therapy in most settings, given its excellent tolerability, generic availability, and evidence base. In the 2026 guideline, ezetimibe is endorsed as a COR 1 intervention for statin-intolerant patients with established ASCVD.

Bempedoic acid (adenosine triphosphate citrate lyase inhibitor) has been formally integrated into the treatment algorithm on the basis of the CLEAR OUTCOMES trial, which demonstrated a significant 13% relative risk reduction in major adverse cardiovascular events (MACE) in a primary and secondary prevention cohort with statin-attributed side effects. It is administered orally once daily and does not cause muscle-related side effects, making it particularly valuable for statin-intolerant patients. Monitoring of uric acid and renal function markers is recommended.

PCSK9 monoclonal antibodies (alirocumab and evolocumab) reduce LDL-C by 45–64% when added to maximally tolerated statin therapy and have demonstrated consistent MACE reduction in very high-risk secondary

prevention (ODYSSEY OUTCOMES and FOURIER, respectively). The 2026 guideline no longer mandates prior ezetimibe use before initiating PCSK9 mAbs, allowing clinician-patient shared decision-making based on degree of LDL-C lowering required, patient preference, and cost.

Inclisiran (small-interfering RNA-based PCSK9 inhibitor) reduces LDL-C by approximately 50% with a favourable dosing schedule of subcutaneous injection at initiation, 3 months, and then every 6 months thereafter. Cardiovascular outcomes trials are ongoing (ORION 4, VICTORION-2 PREVENT), and it is currently designated as a second-line PCSK9 inhibitor (COR 2a) pending outcomes data.

Olezarsen (antisense oligonucleotide apoC-III inhibitor) is a newly recommended agent for patients with familial chylomicronemia syndrome (FCS) and fasting triglycerides ≥1000 mg/dL. In the phase 3 BALANCE trial, olezarsen 80 mg monthly reduced triglycerides by approximately 43.5% compared with placebo and significantly reduced pancreatitis episodes. It carries a COR 1 recommendation as an adjunct to diet in FCS patients.

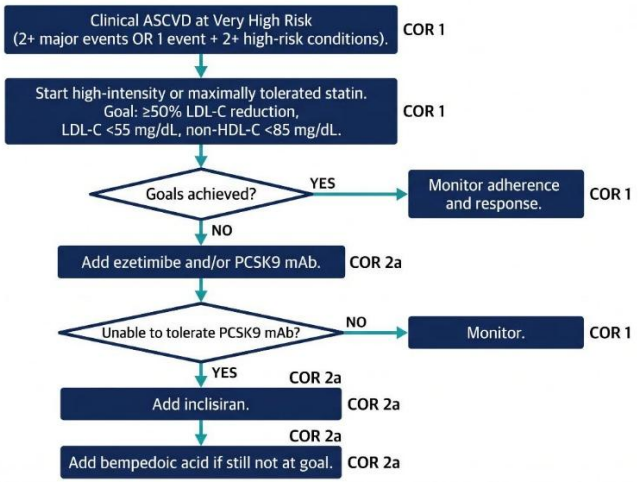


Figure 2. Treatment Algorithm for Secondary ASCVD Prevention at Very High Risk

Table 2. Summary of Key Lipid-Lowering Medications: Mechanism, Efficacy, and Evidence

| Drug Class | Mechanism | LDL-C Reduction | CV Outcomes Trial | Key Clinical Notes |
|---|---|---|---|---|
| Statins (High-Intensity) | Inhibit HMG-CoA reductase → ↑LDL receptors | **≥50%** | Multiple (CTT meta-analysis) | First-line; atorvastatin 40–80 mg or rosuvastatin 20–40 mg preferred |
| Ezetimibe | Blocks NPC1L1 → ↓intestinal cholesterol absorption | **+25% (add-on)** | IMPROVE-IT | Generic; well tolerated; first add-on to statin; COR 1 in statin-intolerant ASCVD |
| PCSK9 mAbs (Alirocumab/Evolocumab) | Monoclonal antibody → ↓PCSK9 degradation of LDL receptors | **45–64%** | FOURIER, ODYSSEY OUTCOMES | SC Q2W or Q4W; no longer requires prior EZE failure; cost declining |
| Bempedoic Acid | ATP citrate lyase inhibitor → ↓hepatic cholesterol synthesis | **21–24% (mono)** | CLEAR OUTCOMES | Oral; no myalgia; monitor uric acid/creatinine; useful in statin-intolerant patients |
| Inclisiran | siRNA → degrades PCSK9 mRNA in hepatocytes | **48–52%** | Pending (ORION 4, VICTORION-2P) | SC Q6 months; HCP-administered; second-line PCSK9i (COR 2a) until CVOT complete |
| Olezarsen | ASO → degrades apoC-III mRNA → ↓TG clearance inhibition | **≃43.5 % TG** | BALANCE (phase 3) | SC Q monthly; COR 1 for FCS with TG ≥1000 mg/dL; reduces pancreatitis |

mAb: monoclonal antibody; ASO: antisense oligonucleotide; TG: triglycerides; FCS: familial chylomicronemia syndrome; EZE: ezetimibe; HCP: healthcare professional; SC: subcutaneous; CVOT: cardiovascular outcomes trial.

## LIPOPROTEIN(A) AND SPECIAL POPULATION HIGHLIGHTS

### Lp(a): Universal Measurement Recommended

Lipoprotein(a) [Lp(a)] is now the subject of a Class I recommendation for measurement at least once in all adult patients for ASCVD risk assessment. This represents a significant paradigm shift, as Lp(a) testing has historically been underutilised. Lp(a) is predominantly determined by the LPA gene and varies substantially by ancestry (highest

concentrations in individuals of African or South Asian descent), with concentrations remaining largely stable throughout adult life, making a single measurement clinically sufficient in most cases.

An Lp(a) concentration of **≥125 nmol/L (≥50 mg/dL)** is considered elevated, associated with approximately a 1.4-fold increased ASCVD risk. Values ≥250 nmol/L (≥100 mg/dL) approximately double ASCVD risk, and values ≥430 nmol/L (≥180 mg/dL) confer approximately 4-fold higher risk—similar to the lifetime risk of heterozygous FH. Elevated Lp(a) should prompt more intensive LDL-C lowering and optimisation of all other modifiable cardiovascular risk factors. PCSK9 mAbs lower Lp(a) by 15–30% as a secondary effect and are the preferred add-on therapy in patients with clinical ASCVD, elevated Lp(a), and unmet LDL-C goals on maximally tolerated statin. Specific Lp(a)-lowering agents (mRNA-targeted and small-molecule inhibitors) are currently in phase 3 cardiovascular outcomes trials.

**Selected Special Population Recommendations**

Several key updates merit attention across clinical subspecialties:

- Persons Living with HIV (PLHIV): The REPRIEVE trial established that pitavastatin 4 mg daily significantly reduced MACE by 35% compared with placebo in PLHIV aged 40–75 years on stable antiretroviral therapy (ART). This has earned a COR 1 recommendation—a landmark development that fills a longstanding evidence gap. Clinicians should be mindful of drug-drug interactions between statins and ART, favouring pitavastatin, rosuvastatin, or pravastatin due to minimal CYP3A4 metabolism.
- Adults with Chronic Kidney Disease (Stage 3+): Moderate-intensity statin or statin-ezetimibe combination is recommended for primary prevention (COR 1). For patients with CKD and established ASCVD, the target is LDL-C <55 mg/dL with high-intensity statin ± ezetimibe and/or PCSK9 mAb (COR 1). Rosuvastatin dose should be reduced in severe CKD (GFR <30 mL/min).
- Adults with Diabetes (40–75 years, no ASCVD): Moderate-intensity statin targeting LDL-C <100 mg/dL remains COR 1. High-intensity statin with target LDL-C <70 mg/dL is reasonable (COR 2a) for those with multiple ASCVD risk factors or at 10-year PREVENT risk ≥10%. IPE (icosapent ethyl) may be considered as an adjunct for persistent hypertriglyceridaemia (150–499 mg/dL) with LDL-C <100 mg/dL on statin.
- Cancer Survivors: Adult cancer survivors with a life expectancy of at least 2 years who otherwise qualify for LLT should be treated similarly to patients without cancer history (COR 1). This new recommendation addresses the well-documented undertreatment of dyslipidaemia in oncology patients.
- Dietary Supplements: The 2026 guideline assigns a COR 3 (No Benefit) recommendation to dietary supplements (including fish oil, red yeast rice, cinnamon, garlic, turmeric, and plant sterols) for lowering LDL-C or triglycerides, based on the SPORT trial showing no significant LDL-C reduction for any supplement compared with placebo. Patient education regarding the absence of evidence supporting supplement use is explicitly encouraged.

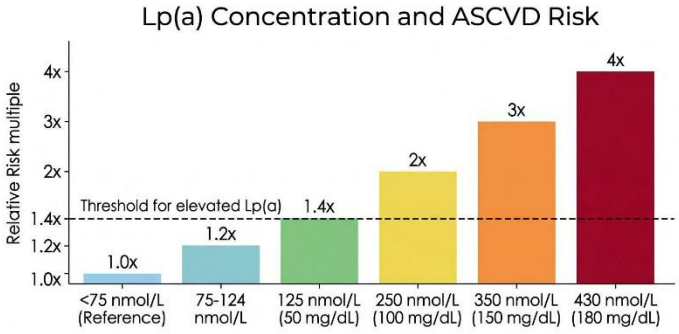


Figure 3. Lp(a) Concentration and ASCVD Relative Risk

**CONCLUSION**

The 2026 ACC/AHA Dyslipidemia Guideline is a comprehensive and practice-changing document that represents a significant advance in evidence-based cardiovascular risk management. For clinicians, its key messages are actionable and clear: use the PREVENT™ equations for contemporary risk estimation; reinstate LDL-C and non-HDL-C numerical treatment targets; measure Lp(a) at least once in all adult patients; leverage CAC scoring to personalise treatment decisions in uncertain cases; and broaden the pharmacological toolkit—including bempedoic acid, PCSK9 inhibitors, and olezarsen—to achieve progressively lower lipid targets in higher-risk patients.

The emphasis on early treatment, longer-term cumulative risk reduction, and shared clinician-patient decision-making is consistent throughout the guideline. Lifestyle modification—including adherence to heart-healthy dietary patterns, regular physical activity, weight management, and tobacco avoidance—remains the indispensable foundation upon which pharmacotherapy is built.

In-house continuing education and clinical governance frameworks should ensure that practising clinicians are upskilled on these updates promptly, with particular attention to risk reclassification tools (PREVENT, CAC), new lipid targets, and the expanded indications for nonstatin therapies. Implementing these guideline recommendations has the potential to meaningfully reduce the burden of ASCVD and premature cardiovascular death in our patient population.

## ABBREVIATIONS

| | | | |
|---|---|---|---|
| **ACC** | American College of Cardiology | **AHA** | American Heart Association |
| **apoB** | Apolipoprotein B | **ART** | Antiretroviral therapy |
| **ASO** | Antisense oligonucleotide | **ASCVD** | Atherosclerotic cardiovascular disease |
| **CAC** | Coronary artery calcium | **CKD** | Chronic kidney disease |
| **CKM** | Cardiovascular-kidney-metabolic | **COR** | Class of Recommendation |
| **CT** | Computed tomography | **CVOT** | Cardiovascular outcomes trial |
| **FCS** | Familial chylomicronemia syndrome | **FH** | Familial hypercholesterolaemia |
| **HDL-C** | High-density lipoprotein cholesterol | **LDL-C** | Low-density lipoprotein cholesterol |
| **LLT** | Lipid-lowering therapy | **Lp(a)** | Lipoprotein(a) |
| **mAb** | Monoclonal antibody | **MACE** | Major adverse cardiovascular events |
| **PCE** | Pooled Cohort Equations | **PCSK9** | Proprotein convertase subtilisin/kexin type 9 |
| **PLHIV** | Persons living with HIV | **PREVENT** | Predicting Risk of Cardiovascular Disease EVENTs |
| **RCT** | Randomised controlled trial | **TG** | Triglycerides |

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## COMPETING INTEREST

The authors declare that they have no competing interests.

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## Review Article

# Novel Oral Anticoagulants: – A Review on Clinical Evolution and Pharmacological Transition

**Devendra Nagar*, Shivankan Kakkar**, Vidhi Rathi***, Dimpy Bansal****, Rahul Jeengar*****, Vishvaranjan Damor******, Rajesh Kasana*******, Hemant Khatana********


## ABSTRACT

**Introduction:** For more than six decades, Vitamin K Antagonists (VKA) drugs were the only available medication for anti-coagulation treatment. The introduction of Direct Acting Oral Anti coagulants (DOACs) has brought a new concept into play. Objective: This study aims to compare the evolution from warfarin treatment to DOACs based on 17 clinical papers.

**Methods:** A literature review was carried out on literature published between 2015 to 2026 on PubMed, Cochrane, Embase and Google Scholar on clinical trials, safety labels, and pharmacological features.

**Results:** It was found that DOACs exhibit better safety, particularly intracerebral hemorrhage, and require no regular laboratory tests.

**Conclusion:** Although VKAs are still applicable in valve disorders, DOACs have become a gold standard in the prevention of stroke and VTE.


**Keywords:** DOACs, Factor IIa, Factor Xa, NOACs, Pharmacology, Warfarin.

## INTRODUCTION

The world of anti-coagulation therapy has experienced the new shift. During the recent time period, the only available option for physicians were Vitamin K Antagonists (VKAs), especially warfarin. Though very effective in decreasing the risks associated with thromboembolism, the efficacy of warfarin is limited due to its narrow therapeutic index and unstable pharmacology, which varies depending on genetic background, dietary habits, and medication interference.

The introduction of novel Oral Anticoagulants (NOACs), currently known as Direct-Acting Oral Anticoagulants (DOACs), initiated the start in current period. By blocking specific enzymes of the blood clotting pathway, Factor Xa and Factor IIa (Thrombin), DOACs deliver a reliable anti coagulation impact. This review will discuss the history of anti-coagulation pharmacology development, highlighting the transition from a complicated specialty procedure to an efficient primary care intervention.

## METHODOLOGY

**Type of Study:** A Review Article.

**Data Sources:** The review is restricted to the 17 articles and clinical guidelines included in the source data that involve major phase III studies (RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48) and meta-analyses related to safety issues.

**Search Strategy:** This literature review was carried out on literature published between 2015 to 2026 on PubMed, Cochrane, Embase, UpToDate and Google Scholar. The keywords used for data extraction were evolution of NOACs, safety of DOACs, Factor Xa inhibitors and warfarin, and indications for NOACs.

**Inclusion Criteria:** Studies on the clinical effectiveness of dabigatran, rivaroxaban, apixaban, and edoxaban; written in English; peer-reviewed clinical studies or reviews.

**Exclusion Criteria:** Animal studies, studies unrelated to oral anticoagulant use, and non-peer-reviewed information.

**Data Extraction Strategy:** Data extraction favored information classified as Critical or Important.

## THE HISTORY OF NOMENCLATURE: FROM NOAC TO DOAC

One of the important parts in history of this, is the nomenclature changes for these drugs.

### The Novel Era (2009-2014)

When dabigatran and rivaroxaban entered the market for the first time, they were classified as NOACs (Novel Oral Anticoagulants). This was done in order to differentiate the new class from the old standard warfarin. However, as the drugs were already well known, the word Novel was soon criticized, as a new drug could not be novel forever and it seems to be negative.

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**The Non Vitamin K Era (2014-2018)**

In order to keep the NOAC acronym and get rid of the word Novel EHRA (part of European Society of Cardiology) suggested a new name: Non-vitamin K antagonist Oral Anticoagulants. It kept the familiar acronym and stressed out the main difference of the drug – its non-interaction with the Vitamin K cycle.

**The Direct-Acting Era (after 2018)**

Today, scientists and ISTH (international society on thrombosis and haemostasis) prefer to call these drugs DOACs (Direct-acting Oral Anticoagulants). The reason for this choice lies in the greater precision of the definition. While Non-Vitamin K described what the drug did NOT do, Direct-acting explains how it worked – through direct enzyme inhibition.

**Origin of the drug name**

**Warfarin:** Derived from the Wisconsin Alumni Research Foundation (WARF) name, where WARF stands for the entity that held the patent on the drug.

**Xaban Suffix:** The Xaban suffix is used to designate Factor Xa inhibitors, as seen in drugs like Rivarixaban and Apixaban.

**Dabigatran:** Gatran suffixes denote DTI drugs.

## EVOLUTION OF ANTICOAGULANTS

**Era of Warfarin**

Anti coagulation was traditionally a reactive approach and since warfarin interferes with the production of Factors II, VII, IX, and X, the onset of action is delayed, making it necessary to use bridging therapy with heparin. INR testing was difficult for clinicians and patients since it required repeated blood collection to maintain the therapeutic window between 2.0–3.0.

**Shift to Direct Inhibition**

This shift happened by the demand for Fixed Dosing,starting with Dabigatran (a Direct Thrombin Inhibitor) and followed by the arrival of Factor Xa inhibitors. Unlike the previous anticoagulants, they did not require bridging and had an early onset of action (2–4 hours).

**Present-day Practice**

The present-day choice for NVAF/VTE includes DOACs as the first-line anticoagulant treatment options. The focus has shifted from how to monitor to how to manage particular patients' safety and profile.

## CLASSIFICATION AND PHARMACOLOGY OF DOACs

According to the presented literature, DOACs can be differentiated into two main pharmacological groups:

**Direct Thrombin Inhibitors (DTI)**

**Dabigatran Etexilate:** A Prodrug, whose activation results in its reversible binding to the thrombin's active site regardless of whether the enzyme is in free or clot-bound form.

**Pharmacokinetics:** 80% renal excretion; absorption highly dependent on acidity of stomach contents.

**Direct Factor Xa Inhibitors**

**Drugs:** Rivaroxaban, Apixaban, Edoxaban.

**Pharmacology:** By blocking the amplification stage of coagulation cascade via the inhibition of Factor Xa, which produces a thrombin burst, the medications from this group prevent blood clot formation.

**Pharmacokinetics:** Rivaroxaban should be taken alongside food, as it provides almost 100% bioavailability. Apixaban has a more stable clearance profile (25% renal) making it a common choice for elderly patients.

**Pharmacodynamics and pharmacokinetics of DOAC (once daily (OD); twice daily (BID); P-glycoprotein (P-gp); area under the curve (AUC); heparin induced thrombocytopenia (HIT); maximum drug concentration in plasma (Cmax)).**

| DOAC | Dabigatran | Rivaroxaban | Edoxaban | Apixaban |
|---|---|---|---|---|
| Target | FIIa | FXa | FXa | FXa |
| t ½ | 12–17 h | 7–13 h | 10–14 h | 8–15 h |
| Cmax | 1–2 h | 2–4 h | 2–4 h | 2–4 h |
| Renal clearance | 80% | 33% active 33% inactive | 50% | 25% |
| Bioavailability | 6% | 80% | 62% | 50% |
| Dosing scheme | BID | OD | OD | BID |
| Interaction | P-gp | CYP3A4, CYP2J2, P-gp | P-gp | CYP3A4 P-gp |
| Interference with food | Prolongs Cmax to 2 h | Increases AUC to 39% | None | None |
| Antidote | Idarucizumab | Andexanet alfa | Andexanet alfa | Andexanet alfa |
| Allowed in pregnancy | No | No | No | No |
| Induces HIT II | No | No | No | No |

**Comparative Analysis**

| Parameter | Warfarin | DOACs |
|---|---|---|
| Target | Multiple Factors (II, VII, IX, X) | Single Factor (Xa or IIa) |
| Dosing | Variable/Titrated | Fixed |
| Monitoring | Frequent (INR Monitoring) | None |
| Onset | 3-5 Days | 1-4 Hours |
| Bleeding risk | High Risk Of ICH | Lower Risk Of ICH |

**Safety & Efficacy:**

One key conclusion comes from all the papers was that DOACs were not only easier to administer but also much safer. All trials reported a statistically significant decrease in the number of intracranial hemorrhages when compared to warfarin. However, while the GI bleeds may differ (high among dabigatran 150 mg and rivaroxaban 20 mg), the benefit of avoiding brain bleeds is the unique pharmacological strength as of now.

## CLINICAL USES

The applications of the drug have changed over time as follows:

1. Prophylactic Orthopedics: Used originally for hip/knee replacement surgery.
2. Stroke Prevention (Atrial Fibrillation): Present day principal indication.
3. Treatment of VTE: Used for acute management and secondary prevention of VTE.
4. Stable Vascular Disease: Rivaroxaban at low dose is now used along with aspirin to treat CAD/PAD.

## DISCUSSION

The progression from NOACs to DOACs shows the success of well-designed molecular chemistry. while the therapeutic advantage of having a shorter half-life is obvious, there is a potential danger in that very same characteristic, and in their adherence. In the past, if a patient missed a dose of warfarin, his or her blood level would remain relatively stable owing to the drugs prolonged half-life. But missing a single dose of a DOAC means that anti coagulation effect came to an end immediately.

## CONCLUSION

The transformation of oral anticoagulants from non-specific VKAs to DOACs has changed the whole safety profile for patients, especially through the decrease in fatal intracranial bleeds. Now the anti-coagulation treatment can be described simply as fixed dose treatment and do not need to monitored regularly and yes, DOACs role in present is not surprising with there compatibility of use; however in developing countries it is still a challenging task of availability of there antidote, if there is any misadventure occur with the use of DOACs ; because of the availability and the price of there antidotes to rural or most urban sectors, their toxicity is unmanageable ; but nevertheless use of DOACs is benefited over risk ratio; however, at last the role of warfarin still holds its own place in valvular heart disease and pregnancy.(not a clear safety profile of DOACs use in pregnancy).

## ABBREVIATIONS

AF: Atrial Fibrillation

AUC: Area Under the Curve

BID: Twice Daily

CAD: Coronary Artery Disease

Cmax: Maximum Plasma Concentration

DOACs: Direct-Acting Oral Anticoagulants

DTI: Direct Thrombin Inhibitor

EHRA: European Heart Rhythm Association

FIIa: Factor IIa (Thrombin)

FXa: Factor Xa

GI: Gastrointestinal

HIT: Heparin-Induced Thrombocytopenia

ICH: Intracranial Hemorrhage

INR: International Normalized Ratio

ISTH: International Society on Thrombosis and Haemostasis

NOACs: Novel Oral Anticoagulants / Non-vitamin K antagonist Oral Anticoagulants

NVAF: Non-Valvular Atrial Fibrillation

OD: Once Daily

P-gp: P-glycoprotein

PAD: Peripheral Artery Disease

VKA: Vitamin K Antagonist

VTE: Venous Thromboembolism

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## Review Article

# Transdiagnostic Neurobiological Mechanisms of Behavioral Addictions A Circuit Based Comparative Review

**Lily Choudhary*, Tanishk Raj**, Shrey Wadhwa***, Shivankan Kakkar****, Vidhi Rathi*****, Dimpy Bansal******


## ABSTRACT

**Introduction:** Behavioural addictions; including gambling disorder, internet gaming disorder, binge eating disorder, compulsive sexual behaviour disorder, marked by compulsive indulgence in reward system activating behaviours in response to internal and external cues, despite their persistent adverse effect. Yet both DSM-5 and ICD-11 classify these disorders using categorical criteria that inadequately reflect their shared neurobiological architecture. In this narrative review, we examine transdiagnostic neurobiological evidence across five behavioral addiction categories through a circuit based comparative analysis of neuroimaging and neuroscientific literature. Searching PubMed and Google Scholar from inception through March 2025, we identified 501 records and, following screening and eligibility assessment, retained 30 studies for synthesis. What emerged was convergent evidence for three interacting domains of circuit dysfunction: dysregulated mesolimbic dopaminergic reward signaling, prefrontal executive control failure, and disrupted fronto striatal connectivity. These abnormalities correspond to the three stages of the addiction cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation and appear to be shaped by trait level vulnerabilities including impulsivity, compulsivity, and reward sensitivity that function as neurobiological endophenotypes. The evidence varies across categories, with gambling disorder the most characterized and buying shopping disorder the least. These findings point toward an integrative circuit level model organized around shared mechanisms rather than categorical boundaries. We suggest that a dimensional framework targeting reward dysregulation, prefrontal inhibitory function, and habit formation offer greater neurobiological validity and stronger trans diagnostic measures.


**Keywords:** Behavioral addictions, Neurobiological mechanisms, Transdiagnostic.

## INTRODUCTION

Behavioral addictions are conditions where compulsive participation in rewarding activities despite adverse consequences, and are increasingly clinically recognised. Gambling disorder, internet gaming disorder, binge eating disorder, compulsive sexual behavior disorder, and buying shopping disorder all also involve the progressive loss of control over a rewarding activity in the absence of any substance use, and all can produce levels of functional impairment and distress similar to substance use disorders. As consumption habits have changed, these behaviours have become more common.

DSM-5 has only gambling disorders within addictive disorders. The ICD-11 includes gaming disorder and compulsive sexual behaviour disorder. Binge eating is part of both the manuals. Buying-shopping disorder is in neither.

Categorical systems divide disorders on the basis of symptom thresholds. Current classification does not imply neural overlap. The same disruptions in mesolimbic reward signaling, in prefrontal regulatory function, in their interconnections are found to be present in both behavioural and behaviours-substance addiction.

Dimensional models conceptualize psychopathology along continuous neurobiological dimensions. Reward valuation, cognitive control, habit formation are overlapping among disorders. Traits like impulsivity, compulsivity, and reward sensitivity capture the individual variation in circuit vulnerability at an endophenotypic level. This review summarises the transdiagnostic neurobiological evidence across five behavioral addiction categories, organizing the analysis around neural mechanisms rather than diagnostic labels. Our study has three goals: to evaluate common circuit dysfunctions, to characterize trait-level endophenotypes, and to assess the

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feasibility of an integrated, clinically meaningful model.

## DIAGNOSTIC FRAMEWORKS AND THE CASE FOR DIMENSIONAL CLASSIFICATION

Grant and colleagues described these conditions as patterns where people continue engaging in rewarding behaviors even as they face serious negative consequences. They feature constant preoccupation, loss of control, increasing tolerance, and withdrawal-like symptoms. This closely resembles the diagnostic line of substance use disorders. Due to this Gambling disorder was reclassified in DSM-5, while ICD-11 includes gaming disorder and CSBD.

The neurobiological profile of CSBD arguably looks more like addiction than other impulse control disorders. Meanwhile, binge eating disorder and buying shopping disorder placed out of the addictive disorder categories in both systems, despite the significant overlap with formally recognised conditions.

Reward system hyperreactivity, prefrontal hypoactivation, fronto striatal disconnection these show up across multiple behavioral addiction phenotypes more or less regardless of which categorical bin the condition has been assigned to. The IPACE model, proposed by Brand and colleagues, captured this mismatch nicely by framing addictive internet use disorders not as discrete entities but as the downstream products of interacting dimensional factors affective states, cognitive biases, executive control failures that operate along a continuum of vulnerability.

The case for dimensional classification, then, is at bottom a neurobiological one. When gambling disorder, internet gaming disorder, binge eating disorder, and compulsive sexual behavior disorder all recruit similar circuit abnormalities, there is a reasonable argument that organizing classification around those mechanisms would be more scientifically valid than continuing to rely on symptom based boundaries that cut across the underlying biology.

## METHODS

### Search Strategy

We searched PubMed and Google Scholar from inception through March 2025 using a combination of disorder related terms (gambling disorder, internet gaming disorder, binge eating disorder, compulsive sexual behavior disorder, buying shopping disorder, behavioral addiction), neurobiological terms (neuroimaging, fMRI, PET, dopamine, reward circuit, striatum, prefrontal cortex, fronto striatal), and mechanistic terms (impulsivity, compulsivity, reward sensitivity, habit formation, addiction cycle). These were combined using Boolean operators across conceptual domains.

### Inclusion and Exclusion Criteria

Studies were eligible if they used neuroimaging, neurochemical, or connectivity methods in adult human populations and reported findings bearing on reward processing, executive control, or fronto striatal connectivity in at least one of the five target conditions. We included original neuroimaging studies, systematic reviews, meta analyses, and mechanistic investigations. We excluded Studies restricted to adolescent only samples, single case reports, and papers without neurobiological outcomes.

### Study Selection and Data Extraction

Our search initially identified 501 records. After carefully screening titles and abstracts, we reviewed the full texts of the most relevant studies and ultimately included 30 in our thematic synthesis. We extracted key information such as the mural regions involved, neurotransmitter findings. Patterns of functional and structural connectivity were noted. Methodologies were reviewed. Findings were control grouped into three main circuit domains: reward circuitry, fronto-striatal connectivity, and executive.

## REWARD CIRCUIT DYSFUNCTION ACROSS BEHAVIORAL ADDICTIONS

### Dopaminergic Reward Signaling and Prediction Error

Mesolimbic dopamine plays a central role in reward prediction error, demonstrated by Schultz. Dopaminergic neurons signal expected vs actual rewards. Dysregulation leads to compulsive behaviour. This occurs via the mesolimbic pathway linking the ventral tegmental area, nucleus accumbens, and prefrontal cortex.

Linnet and colleagues showed that in gambling disorders, dopamine release in the ventral striatum is altered. At the same time, activity in the orbitofrontal cortex is increased. This implies improper linking of reward signals with value-based decision-making. Volkow and colleagues identified dopamine D2 receptor levels are lower across addictions. This weakens inhibitory control, increasing the compulsive behavior.

Schott and colleagues demonstrated dopamine responses in the ventral striatum during reward anticipation. They depend on frontostriatal connectivity. These are disrupted in internet gaming disorder. In binge eating disorder, strong ‘wanting’ but reduced ‘liking’ shows a mismatch in reward processing.

### Ventral Striatal Hyper and Hyporeactivity

The nucleus accumbens helps to decide how rewarding something feels. Compulsivity showing increased ventral striatal activation in response to specific cues has been reported across gambling disorder, compulsive sexual behavior disorder, and binge eating disorder. This pattern aligns with incentive sensitization theory. Here, cues acquire exaggerated motivational salience.

Wang and colleagues found lower striatal responses to non-addiction-related rewards in internet gaming disorder. This is called generalized reward hyposensitivity.

Similar dissociation is widely documented in substance addiction. It reinforces the transdiagnostic nature of this mechanism.

### Reward Salience and Mesolimbic Connectivity

Mesolimbic pathway links the ventral tegmental area, nucleus accumbens, amygdala, and prefrontal cortex. It helps assign importance to different stimuli.

Research by Schott and colleagues shows dopamine activity in striatum affects reward signalling. In gambling disorder and internet gaming disorder, this communication is weaker. This leads to impulsivity. Meyer and colleagues found the link in increased dopamine release during gambling and abnormal activity in the orbitofrontal cortex. This explains decision-making was impaired. Choices are no longer based on careful evaluation. Behaviour was shifting towards a habit-like pattern driven by salience. Across disorders, similar connectivity disruptions are seen.

## FRONTOSTRIATAL DYSREGULATION AND CONNECTIVITY ALTERATIONS

### Prefrontal Cortex Dysfunction and Inhibitory Control Failure

The PFC helps allow a person to weigh immediate rewards against longer-term consequences. Goldstein and Volkow's iRISA model captures that the prefrontal cortex is not functioning properly. Two things happen at once: the brain is less able to control impulses. Simultaneously, addiction-related cues become more powerful.

Activity in the prefrontal cortex is reduced, affecting decision-making. This includes both ventromedial and dorsolateral regions. It is seen during reward-related tasks in gambling disorder.

Yao and colleagues carrying out research on internet gaming disorder found frontal hypoactivation. This happens during inhibition tasks. There is also a decrease in prefrontal grey matter.

The meta-analytic evidence of Luijten and colleagues combined neuroimaging data across different types of addiction. They found a pattern: reduced activity in the right inferior frontal gyrus and anterior cingulate cortex. These regions are crucial for inhibitory control. This pattern appeared in both substance or a behavioral addiction. Wang and colleagues showed weaker connectivity between frontal and striatal regions. This happens during inhibition tasks in affected individuals. The strength of this connectivity was inversely related to compulsivity.

### Frontostriatal Connectivity Alterations Across Disorders

The network of connections between brain regions become altered. The prefrontal cortex, anterior cingulate, and striatal regions are involved. Park and colleagues found reduced resting-state connectivity between the dorsolateral prefrontal cortex and the caudate. More severe cases show greater disconnection. Wang and colleagues reported weakened communication between the orbitofrontal cortex and striatum during reward anticipation. Kühn and Gallinat observed both structural and functional changes in frontostriatal circuits.

Trotzke and colleagues found that affected individuals display altered orbitofrontal and ventromedial prefrontal cortex. People struggle to weigh long-term consequences against immediate rewards.

Frontostriatal hypoconnectivity is the common finding in the behavioral addiction literatures.

### Habit Formation and the Shift Toward Compulsion

In the early stages, addictive behaviors are usually goal-directed. Over time it becomes compulsive.

With repeated engagement, control gradually shifts toward the dorsolateral striatum, which encodes automatic stimulus–response habits that operate with little regard for outcomes.

Everitt and Robbins reported that as prefrontal control weakens, it loses its ability to regulate dorsal striatal habit circuits.

Elevated dorsal striatal activation during disorder-relevant cues has been reported in gambling disorder and internet gaming disorder. It also showed the dorsal caudate engagement correlating with behavioral automaticity and reduced sensitivity to loss feedback.

Compulsivity is an emergent property of progressive frontostriatal dysregulation, a process in which habit circuits gradually win out over executive control.

## TRANSDIAGNOSTIC CONVERGENCE

### Trait Vulnerabilities as Neurobiological Endophenotypes

According to neurobiological literature, there are three trait dimensions: impulsivity, compulsivity, and reward sensitivity. They appear to function as endophenotypes predisposing individuals to addiction.

Luijten and colleagues demonstrated that impulsivity is associated with hypoactivation of the right inferior frontal gyrus and anterior cingulate cortex during response inhibition. This pattern is consistent across behavioral and substance addictions. Raised impulsivity precedes disorder onset according to some longitudinal literature.

Compulsivity reflects the elevated dorsal striatal habit circuits and reduced prefrontal control. It has been framed by Robbins and Clark as a transdiagnostic dimension

linking addictions with obsessive–compulsive spectrum disorders. It is associated with disorders such as gambling and compulsive sexual behavior.

Reward sensitivity provides the motivational drive to engage in addictive behaviors. Volkow and colleagues linked heightened cue reactivity to reduced dopamine D2 receptor availability.

The interaction of high reward sensitivity, impaired inhibitory control, and strong habit formation facilitates the transition from impulsive to compulsive behavior.

### StageWise Mechanisms Across the Addiction Cycle

Koob and Volkow proposed a three-stage model of addiction: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation, driven by progressive circuit dysregulation.

The binge stage is characterized by increased mesolimbic dopamine activity, with heightened ventral striatal activation during engagement.

Evidence for the withdrawal stage in behavioral addictions remains limited, though clinical features such as irritability and low mood suggest partial overlap with substance-related negative affect states.

The preoccupation stage reflects craving and relapse due to an imbalance between heightened striatal cue reactivity and reduced prefrontal inhibitory control.

### Behavioral Versus Substance Addiction: What Overlaps and What Does Not

Behavioral and substance addictions show significant neurobiological overlap. Kühn and Gallinat demonstrated that both share heightened ventral striatal cue reactivity. However, reduced prefrontal control, and disrupted frontostriatal connectivity is also seen. Common mechanisms include dopamine dysregulation, altered reward prediction error signaling, and increased reliance on dorsal striatal habit circuits.

Substance addictions involve direct pharmacological effects on neurotransmitter systems. These are absent in behavioral addictions.

## AN INTEGRATIVE NEUROBIOLOGICAL MODEL

Elevated reward sensitivity overreacts to disorder-related stimuli. Impulsivity reflects reduced prefrontal inhibitory control. Compulsivity via dorsal striatal habit systems, create the shift to automatic responding. These traits interact synergistically.

Neuroimaging findings support this model in gambling disorder more than in buying shopping disorder.

Interventions targeting dopamine signaling may have transdiagnostic relevance. It supports a biologically grounded treatment model.

## LIMITATIONS AND FUTURE DIRECTIONS

### Limitations

First, direct comparability is limited due to marked methodological differences across studies. Which includes variabilities in task design, imaging techniques, and diagnostic criteria.

Second, most studies are cross-sectional with small sample sizes. It is unclear if changes are causes or effects.

Third, the withdrawal/negative effect stage is not well understood. It is less clear as compared to substance use disorders. The reason may be true differences or lack of research.

Fourth, the evidence is uneven across behavioral addiction categories. Gambling disorder and internet gaming disorder are most researched. Binge eating disorder and buying–shopping disorder are less studied. This can bias conclusions.

Finally, comparisons with substance addiction are indirect. They rely on parallel literature.

### Future Directions

Longitudinal neuroimaging studies track brain changes. They show how circuits change as an illness progresses. Computational methods study reward prediction error. They help explain dopamine function.

Neuromodulation techniques can be used. For example, transcranial magnetic stimulation targets the dorsolateral prefrontal cortex. They may reduce compulsive behavior. This supports weak prefrontal control over reward circuits.

Finally, there is a need for dimensional biomarker development. These include ventral striatal reactivity, frontostriatal connectivity, and reward sensitivity. These come from neuroimaging and computational modeling. Such measures could enable early identification of high-risk asymptomatic individuals.

## CONCLUSION

The evidence reinforces shared circuit-level dysfunction across behavioral addictions. Across multiple disorders, similar mesolimbic changes are seen. These include problems in frontostriatal connectivity and prefrontal control. Not every condition fits the model well.

Different conditions may share the same brain circuit. So, classification systems should be mechanism-based. These would focus on dimensions like reward processing, cognitive control, and habit formation.

This approach may be more scientifically accurate and clinically useful. The current system treats mechanism shared conditions as completely separate diagnoses. Key traits like impulsivity, compulsivity, and reward sensitivity

can be measured. They provide biological markers and reflect inherited vulnerability.

## ABBREVIATIONS

DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5th edition)

ICD-11: International Classification of Diseases (11th revision)

CSBD: Compulsive Sexual Behavior Disorder

IPACE model : Interaction of Person-Affect-Cognition-Execution model

fMRI : Functional Magnetic Resonance Imaging

PET : Positron Emission Tomography

PFC : Prefrontal Cortex

iRISA model : Impaired Response Inhibition and Salience Attribution

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## AVAILABILITY OF DATA AND MATERIALS

Data will be available by emailing lily.leexe@gmail.com

## AUTHORS' CONTRIBUTIONS

Author*: participated in the investigation, conceptualization, methodology, resources, validation, writing, reviewing, and editing.

Author**: participated in the investigation, conceptualization, and data collection.

Author***: corresponding author participated in data collection, supervision, and editing.

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## ETHICS APPROVAL

The narrative review is exempt from ethics approval as it is based entirely on previously published literature and it does not involve primary data collection from human participants.

## COMPETING INTEREST

The authors declare that they have no competing interests.

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## Review Article

# Weight Regain and Cardiometabolic Reversal following Discontinuation of Incretin Based Therapies A Review

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## ABSTRACT

**Background:** Incretin-based therapies, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual GIP/GLP-1 agonists have been efficacious in obesity management. However, obesity being a chronic disease requires long term pharmacological interventions to manage it.

**Objective:** To evaluate the magnitude, timeline, and physiological mechanisms of weight regain and cardiometabolic reversal following the withdrawal of semaglutide, tirzepatide, and other GLP-1 RAs based on clinical trials evidence.

**Methods:** A comprehensive literature search was conducted across PubMed, MEDLINE, Cochrane and Google Scholar for articles published between 2022 and 2026 and review was conducted on 24 selected academic papers, including significant randomized withdrawal trials (STEP 1, STEP 4, SURMOUNT-4) and recent systematic reviews.

**Results:** Upon treatment withdrawal, patients typically experience a rapid weight rebound, regaining approximately two-thirds of lost weight within one year. This regain is accompanied by a significant reversal of improvements in blood pressure, glycemic control, and lipid profiles. Key drivers include neurobiological changes, persistent metabolic adaptations, and the return of food cravings.

**Conclusion:** Obesity requires long term care. Current evidence indicates that the metabolic benefits of GLP-1-based therapies are largely transient upon discontinuation, making long-term maintenance strategies necessary.

**Keywords:** GLP-1 Agonist discontinuation, GLP-1 Agonist Withdrawal, Semaglutide withdrawal, Weight Rebound, Weight Regain.

## INTRODUCTION

Obesity is a widespread complex, chronic, and relapsing metabolic disease marked by abnormal or excessive fat accumulation that adversely affects health, increasing the risk of metabolic, cardiovascular and Musculoskeletal disorders. With the development of highly effective incretin-based therapies such as semaglutide, a GLP-1 receptor agonist (RA), and tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and other GLP-1 RA, the treatment strategies have shifted, achieving weight loss previously seen only with bariatric surgeries. Despite these advances, real world data suggest high rates of treatment discontinuation due to cost, side effects, or a perceived cure. This has led to a critical clinical question: what happens to metabolic health once these potent agents are withdrawn? This review combines findings from 24 key studies to explain weight rebound after stopping treatment and the physiological reasons behind it.

## METHODS

A comprehensive literature search was conducted across PubMed, MEDLINE, Cochrane and Google Scholar for articles published between 2022 and 2026.

Screening was done using Boolean operators ((GLP-1 RA OR Semaglutide OR Liraglutide OR Tirzepatide) AND (Weight Regain OR Rebound OR Discontinuation OR Withdrawal)).

24 key research papers were included. The literature focus was specifically on the discontinuation period following successful weight loss.

### Inclusion Criteria

Peer reviewed clinical trials (e.g., STEP and SURMOUNT programs); systematic reviews; meta-analyses; studies with >= 20 weeks of active treatment followed by a documented withdrawal phase; written in English.

### Exclusion Criteria

Case reports; letters to editor; animal models; studies without post discontinuation weight data; non-english publications.

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## MECHANISMS OF WEIGHT REGAIN AFTER GLP-1 WITHDRAWAL

The rapid regain of weight post-discontinuation is because of potent biological counter- regulatory mechanisms triggered by weight loss.

### Neurobiological Rebound: The Food Noise

GLP-1 RAs act centrally on the hypothalamus and hindbrain to increase satiety and reduce the pleasure you feel from food.

Upon withdrawal, patients report a rapid return of food cravings, intrusive thoughts about eating and a surge in appetite. This is linked to the loss of exogenous appetite inhibition while the brain's reward pathways remain sensitized.

### Metabolic Adaptation

Weight loss induces adaptive thermogenesis, where resting energy expenditure (REE) decreases beyond what is predicted by the loss of body mass. This metabolic slowdown often persists after the drug is stopped, creating a metabolic gap where energy intake easily exceeds energy expenditure.

High hunger + Low BMR = Rapid fat accumulation.

### Hormonal Dysregulation

During GLP-1 RA therapy, satiety hormones like leptin decrease while the hunger hormone ghrelin increases. When the pharmacological satiety signal is removed, the body is left in a state of high hunger and low satiety, causing hyperphagia and rapid adipose tissue accumulation.

### Behavioral Rebound

There may be increased caloric intake after stopping the drug.

## EVIDENCE FROM CLINICAL TRIALS

The clinical understanding of weight regain is primarily derived from randomized withdrawal trials.

### The STEP Program (Semaglutide)

In the STEP 1 extension trial, participants who completed 68 weeks of semaglutide 2.4mg regained two-thirds of their lost weight within 52 weeks of stopping the drug. Mean weight loss decreased from 17.3% at week 68 to only 5.6% at week 120. In the STEP 4 trial, those switched to placebo at week 20 regained 6.9% of their body weight by week 68, while the continuation group lost an additional 7.9%.

### The SURMOUNT Program (Tirzepatide)

The SURMOUNT-4 trial followed a 36-week lead-in phase. Patients switched to placebo regained 14.8% of their weight by week 88, whereas the continuation group achieved a total weight loss of 25.3%. This demonstrates that dual agonists also result in significant regain upon cessation.

## MAGNITUDE AND TIMELINE OF WEIGHT REGAIN

Weight regain following incretin therapy is rapid and significant.

**Timeline**: Regain begins almost immediately, often within 4 to 8 weeks of the last dose. The most aggressive regain phase occurs in the first 6 months. Meta regression analyses indicate that weight regain does not plateau immediately after treatment cessation but progressively trends towards baseline over the first year.

**Magnitude**: Meta-analyses suggest that without alternative intervention, patients regain approximately 1% to 1.5% of their body weight per month following discontinuation. At one year off-drug, the average regain is approximately 60–70% of the total weight lost during treatment.

## METABOLIC CONSEQUENCES AFTER DISCONTINUATION

The rebound involves a systemic reversal of cardiometabolic improvements.

### Cardiovascular Parameters

In the SURMOUNT-4 and STEP 1extension trials, the withdrawal of therapy led to a significant increase in systolic and diastolic blood pressure. Those who regained the most weight saw a near total reversal of the antihypertensive benefits.

### Glycemic and Lipid Profiles

HbA1c levels and fasting insulin trend back toward pre-treatment levels upon cessation. Initial improvements in triglycerides and LDL cholesterol are largely lost as adipose tissue is regained.

## KEY CLINICAL TRIALS AND WEIGHT REGAIN TRAJECTORIES

Table 1: Key Clinical Trials and Findings

| Author /Year | Drug | Trial Name | Withdrawal Duration | Main Findings Post-Withdrawal |
|---|---|---|---|---|
| Wilding et al. (2022) (1) | Semaglutide | STEP 1 Extension | 52 Weeks | Regained two-thirds of lost weight; reversal of blood pressure and lipid improvements. |
| Horn et al. (2025) (8) | Tirzepatide | SURMOUNT-4 | 52 Weeks | 14.8% weight regain; significant reversal of cardiometabolic benefits. |

| | | | | |
|---|---|---|---|---|
| Jensen et al. (2024) (10) | Liraglutide | Post-RCT Study | 52 Weeks | Supervised exercise during treatment helped maintain some fat loss post-drug. |
| Garvey et al. (2022) (11) | Semaglutide | STEP 5 | 104 Weeks | On-treatment group: Maintained 15.2% weight loss through 2 years with continuous use. |
| Quarenghi et al. (2025) (4) | Multiple | Narrative Review | Various | Confirmed consistent rebound across semaglutide, liraglutide, and tirzepatide. |

Table 2: Estimated Weight Regain Magnitude and Physiological Status

| **Months Post-Cessation** | **Estimated Regain (% of initial loss)** | **Physiological and Behavioral Status** |
|---|---|---|
| 0-3 Months | 15-20% | Rapid return of "food noise" and hedonic hunger; loss of exogenous satiety. |
| 3-6 Months | 30-45% | Active accumulation of adipose tissue; metabolic adaptation limits energy outlay. |
| 6-12 Months | 60-70% | Weight trajectory trends toward pre-treatment set point; stabilization of regain. |
| >12 Months | >70% | Potential return to baseline weight without secondary maintenance interventions. |

## COMPARISON BETWEEN SEMAGLUTIDE AND OTHER GLP-1 RAs

While all incretin-based therapies show a rebound effect, the absolute magnitude varies.

Tirzepatide vs. Semaglutide: Tirzepatide achieves greater initial loss, so the absolute weight regained in kilograms can be higher, though the percentage of regain relative to loss is similar.

Liraglutide: As a less potent daily injectable, liraglutide shows a similar regain curve, though the total weight regained is lower in absolute terms because the initial loss was less.

## CLINICAL IMPLICATIONS

Obesity must be managed as a chronic condition.

**Chronic Therapy:** Clinicians must counsel patients that these medications are long-term treatments.

**Maintenance Strategies:** Regular exercise and switching to oral anti-obesity drugs may help to reduce weight regain.

## CONCLUSION

Withdrawal of GLP-1 RAs leads to a rapid regain of weight and reversal of metabolic benefits. This shows that chronic treatment model is necessary for obesity. Limitations are that most trials are limited to one year of follow-up. Data on tapering strategies are largely missing from provided studies.

A critical lack of structured support exists for patients who must stop medication, often leading to unmonitored rebound obesity.

Future Directions for mitigating the rebound are:

- Combined Exercise: Identifying responders who can maintain weight through lifestyle alone is a priority. Supervised resistance training during treatment helps preserve fat-free mass and maintain a higher basal metabolic rate.
- Pharmacological Tapering: Gradual dose reduction or transitioning to metformin as a step-down strategy may help reduce eight regain.
- Guided Support: Behavioral and digital tools to help patients manage the transition period.

## ABBREVIATIONS

BMR: Basal Metabolic Rate

GIP: Glucose-Dependent Insulinotropic Polypeptide

GLP-1: Glucagon-Like Peptide-1

GLP-1 RAs: Glucagon-Like Peptide-1 Receptor Agonists

HbA1c: Glycated Hemoglobin

LDL: Low-Density Lipoprotein

RA: Receptor Agonist

RCT: Randomized Controlled Trial

REE: Resting Energy Expenditure

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## CPC Update

# Macronodular Hepatic Tuberculosis - The Radiological Masquerader Tale of Diagnosis and Post-Treatment Surveillance

**Parul Gupta*, Meenu Bagarhatta**, Anu Bhandari***, C. P. Swarnkar******


## ABSTRACT

Hepatic tuberculosis is a rare extrapulmonary form of tuberculosis that may closely simulate primary and secondary hepatic malignancies on cross-sectional imaging. We report a 34-year-old woman who presented with chronic right hypochondrial pain, anorexia, and significant weight loss, and was found on multimodality imaging to have a solitary subcapsular right hepatic lesion exhibiting thick peripheral rim enhancement without washout, progressive delayed centripetal filling-in, overlying capsular retraction, T2 hypointense foci, and patchy diffusion restriction — features indistinguishable from mass-forming cholangiocarcinoma. Ultrasound-guided core biopsy demonstrated caseating granulomas with acid-fast bacilli, confirming hepatic tuberculosis. The patient completed nine months of first-line anti-tubercular therapy with documented radiological resolution, yet re-presented 10 months after treatment completion with constitutional symptoms and radiological progression of hepatic lesions. Repeat biopsy revealed caseating granuloma with negative GeneXpert MTB/RIF (CBNAAT), highlighting the limited sensitivity of nucleic acid amplification in paucibacillary post-treatment solid-tissue samples, with mycobacterial liquid culture awaited. This case underscores the importance of histopathological confirmation for atypical hepatic masses, microbiological evaluation in suspected tuberculosis cases and draws attention to the diagnostic pitfalls of CBNAAT in post-ATT surveillance biopsies.


**Keywords:** Hepatic tuberculosis, Cholangiocarcinoma mimic, Capsular retraction, CBNAAT, GeneXpert MTB/RIF, Paucibacillary, Recurrent tuberculosis, Paradoxical reaction.

## INTRODUCTION

Tuberculosis remains a major global health burden, with extrapulmonary involvement in up to 15–20% of cases. Isolated hepatic tuberculosis without miliary dissemination or overt pulmonary disease is rare, accounting for less than 1% of all tuberculosis cases. Its localized macronodular (pseudotumoral) form is particularly challenging, closely mimicking mass-forming cholangiocarcinoma, metastases, and inflammatory pseudotumours on imaging and frequently leading to delayed diagnosis or unnecessary hepatic resection. Furthermore, GeneXpert MTB/RIF (CBNAAT), despite being the recommended initial molecular test for extrapulmonary tuberculosis (EPTB), suffers from reduced sensitivity in paucibacillary solid-tissue samples, particularly in post-treatment surveillance settings. We report a case that combines both these diagnostic dilemmas.

## CASE REPORT

A 34-year-old woman was referred for abdominal ultrasonography with a one-year history of insidious, diffuse, dull-aching abdominal pain predominantly in the right hypochondrium, exacerbated postprandially, along with unintentional weight loss of 8–10 kg, anorexia, weakness, and fatigue. She denied fever, night sweats, jaundice, altered bowel habits, or prior tuberculosis contact. Past, personal, and family histories were unremarkable.

On examination, she was afebrile and haemodynamically stable (BMI 17.2 kg/m²), with mild right hypochondrial tenderness and a firm, smooth hepatomegaly palpable 3 cm below the right costal margin (liver span 15 cm). Complete blood counts, liver function tests, renal function, viral markers, and tumour markers were within normal limits, with an isolated elevation of the erythrocyte sedimentation rate.

## INITIAL IMAGING FINDINGS

Greyscale sonography demonstrated mild hepatomegaly with a well-defined 45 × 35 mm hypoechoic subcapsular lesion in the right hepatic lobe with internal vascularity on colour Doppler (Figure 1). Triple-phase contrast-enhanced computed tomography (TPCT) showed an iso- to hypodense subcapsular lesion involving segments VI, VII, and VIII with subtle overlying capsular retraction; the lesion exhibited thick, complete peripheral rim enhancement on the late arterial phase, persistent rim enhancement without washout on the portovenous phase,

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and minimal patchy central enhancement on the delayed phase (Figure 2). Triple-phase MRI (TPMRI) confirmed a T2 hyperintense lesion with internal T2 hypointense foci, patchy peripheral diffusion restriction, and dynamic post-contrast thick peripheral rim enhancement with progressive centripetal filling-in on delayed phases (Figure 3) — features jointly favouring mass-forming cholangiocarcinoma or an inflammatory pseudotumour over hepatocellular carcinoma.

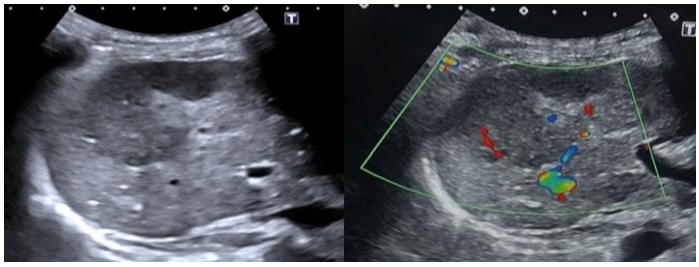
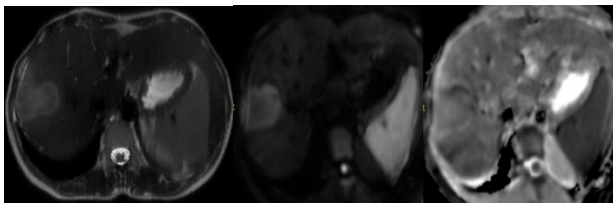


Figure 1: Greyscale and colour Doppler ultrasonography of the abdomen demonstrating a well-defined 45 × 35 mm hypoechoic subcapsular lesion in the right hepatic lobe with internal vascularity. No calcification/hyperechoic areas within. No biliary dilatation or capsular retraction evident. No regional LN or ascites.

Figure 2: TPCT of the abdomen at initial presentation. (A) Axial non-contrast image showing a subcapsular hypodense lesion in segments VI–VIII with overlying capsular retraction. (B) Late arterial phase demonstrating thick, complete peripheral rim enhancement with a non-enhancing centre. (C) Portovenous and (D) delayed phases showing persistent rim enhancement without washout and minimal patchy central enhancement.



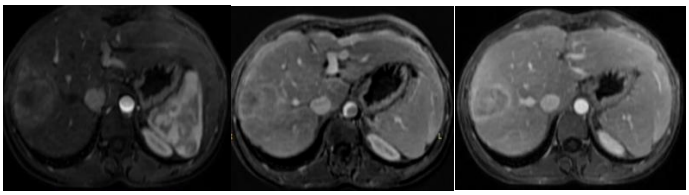


Figure 3: TPMR of the liver at initial presentation. (A) Axial T2-weighted image showing a predominantly hyperintense lesion with internal hypointense foci. (B) DWI and (C) ADC map demonstrating patchy peripheral diffusion restriction. (D–F) Dynamic post-gadolinium arterial, portovenous, and delayed phase images showing thick peripheral rim enhancement with progressive centripetal filling-in without washout. Delayed-phase images also demonstrate lacy septal enhancement between granulomas.

## INITIAL TISSUE DIAGNOSIS AND TREATMENT

Ultrasound-guided percutaneous core biopsy using a 16–18 G automated needle yielded multiple cores showing distortion of hepatic architecture, ballooning degeneration, and multiple caseating granulomas surrounded by lymphocytes and plasma cells. Acid fast bacilli were seen with Ziehl Neelsen diagnosing the lesion as hepatic tuberculosis (Figure 4). High-resolution CT of the chest was performed to rule out pulmonary involvement and was found to be negative. The patient was diagnosed as isolated primary macronodular type of hepatic tuberculosis and was initiated on first-line, weight-based, four-drug anti-tubercular therapy (ATT) per national guidelines for nine months. End-of-treatment TPCT demonstrated complete radiological resolution of the hepatic lesion (Figure 5), and ATT was stopped.

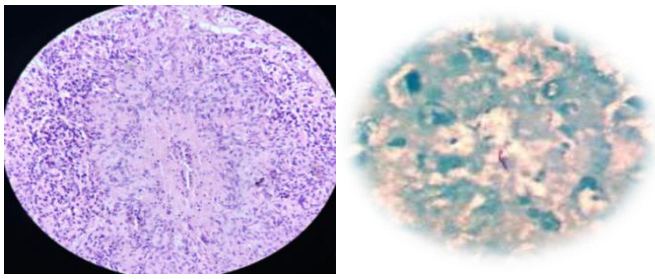


Figure 4: Photomicrograph of the initial ultrasound-guided core biopsy showing caseating epithelioid cell granulomas surrounded by lymphocytes and plasma cells, with acid-fast bacilli demonstrable on Ziehl–Neelsen staining.

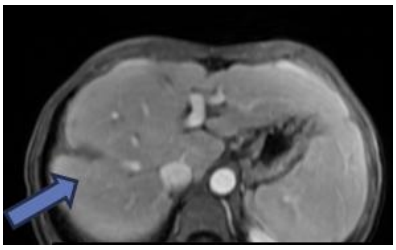


Figure 5: Contrast enhanced MR Images showing resolution of the lesion with just a fibrotic band.

## RECURRENCE AND SECOND WORK-UP

Approximately ten months after ATT completion, the patient re-presented with low-grade evening fever, recurrent abdominal pain, persistently poor appetite, and static weight. Laboratory work-up revealed a re-elevated ESR, hypoalbuminaemia, and a reversed albumin:globulin ratio. Repeat TPMRI demonstrated multiple hepatic lesions, conglomerate mildly enhancing upper abdominal lymphadenopathy along with mild splenomegaly and ascites (Figure 6). A repeat ultrasound-guided core biopsy was performed, with samples dispatched in both formalin (for histopathology) and sterile normal saline (for microbiology). GeneXpert MTB/RIF (CBNAAT) on the hepatic biopsy was negative, and the sample was inoculated into MGIT liquid culture for mycobacterial growth and drug-susceptibility testing (result awaited). Differential considerations at this stage included drug-resistant tuberculosis, paradoxical reaction, and non-tubercular granulomatous conditions such as sarcoidosis, fungal infection (histoplasma), and lymphoma. In accordance with current recommendations, empirical re-initiation of ATT was deferred pending microbiological confirmation, and multidisciplinary evaluation was planned.

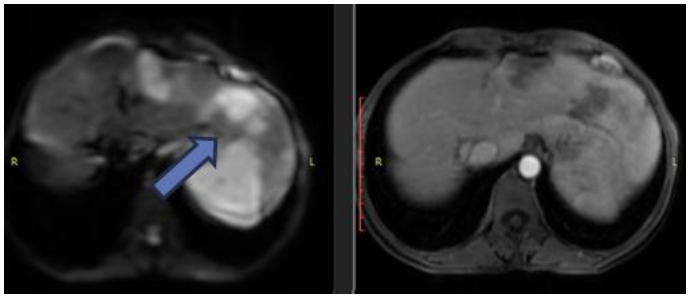


Figure 5: Contrast enhanced MRI abdomen revealed new hepatic lesions in both lobes of liver with rim enhancement

## DISCUSSION

Hepatic tuberculosis is classified into miliary, granulomatous, and localized (macronodular) forms, the last being rarest and most prone to misdiagnosis as malignancy. Imaging clues that may favour tuberculosis over malignancy include T2 hypointensities corresponding to caseating granulomas, absence of arterial washout, progressive delayed central/lacy septal enhancement reflecting fibrous stroma rather than necrosis, traversing rather than displaced vessels, and concurrent splenic granulomas.

GeneXpert MTB/RIF is the recommended initial molecular test for EPTB, with rapid turnaround and simultaneous rifampicin-resistance detection. However, its sensitivity in solid-tissue EPTB samples, particularly hepatic biopsies, is highly variable (37–93%) because these lesions are paucibacillary; after ATT, the bacillary load falls below the assay's detection limit (~131 CFU/ml), further reducing yield in post-treatment surveillance. Formalin fixation itself reduces sensitivity by 15–20%, reinforcing the need to dispatch a portion of every suspected EPTB biopsy in sterile normal saline before fixation. Empirical reintroduction of ATT on clinic-radiological grounds alone is discouraged; current guidance mandates comprehensive repeat work-up — histopathology, AFB smear, mycobacterial culture with drug-susceptibility testing, CBNAAT/line probe assay, and fungal stains — to distinguish true relapse, drug resistance, paradoxical reaction, and alternative granulomatous disease.

## CONCLUSION

Hepatic tuberculosis is a formidable radiological mimicker of hepatobiliary malignancy, and its diagnosis rests on histopathological confirmation. Recurrent hepatic lesions following apparent radiological cure demand rigorous microbiological re-evaluation rather than empirical retreatment, and clinicians should be aware of the reduced sensitivity of CBNAAT in paucibacillary post-ATT solid-tissue samples. Dispatching a portion of the biopsy in sterile saline for mycobacterial culture and drug-susceptibility testing should be standard practice in all suspected cases of extrapulmonary tuberculosis.

## ABBREVIATIONS

CBNAAT: Cartridge Based Nucleic Acid Amplification Test

EPTB: Extrapulmonary tuberculosis

TPCT: Triple-phase contrast-enhanced computed tomography

TPMR: Triple-phase Magnetic Resonance Imaging

ATT: Anti-tubercular therapy

## DECLARATION OF ACKNOWLEDGMENT

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## AVAILABILITY OF DATA AND MATERIALS

Data will be available by emailing parul10gupta@yahoo.co.in

## AUTHORS' CONTRIBUTIONS

Author*(Corresponding Author): Conceptualization, investigation, image interpretation, and manuscript drafting.

Author**: Clinical data collection, literature review, and manuscript drafting.

Author***: Validation of radiological findings, Supervision, methodology, critical review, and final editing.

Author****: Participated in writing, reviewing, and editing.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

## ETHICS APPROVAL

The study adhered to the ethical principles of the Declaration of Helsinki (1964) and its subsequent amendments. As this is a single-patient case report, formal ethics committee approval was not required. Written informed consent was obtained from the patient for publication of her anonymized clinical details and imaging findings.

## COMPETING INTEREST

The authors declare that they have no competing interests.

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## Case Report

# Epidermal inclusion Cyst Masquerading as a Supernumerary Testicle

**Mukesh Mittal*, Pankaj Kumar Nitharwal**, Rahul Sharma***, Ayush Gupta****, Kavita Redu*****


### ABSTRACT

Epidermal inclusion cysts are lined by stratified squamous epithelial wall and filled with laminated keratin, cholesterol crystals and debris. Epidermal inclusion cysts are benign cysts which occur after implantation of epidermal tissue into the dermis or subcutaneous tissues. Scrotal epidermal inclusion cysts usually occur in the midline along the median raphe presents as a painless, midline, firm, freely mobile extra-testicular mass. Scrotal epidermal inclusion cysts can mimic supernumerary testicle, complex cystic and neoplastic pathologies on USG. We present a case of 42-year-old male with painless midline scrotal swelling which was mimicking supernumerary testicle on USG. After complete surgical excision, histopathological examination confirmed a benign epidermal inclusion cyst.


**Keywords:** pseudotestis, inclusion cysts, supernumerary testicle.

### INTRODUCTION

Epidermal inclusion cyst in the scrotum usually presents as a painless, midline, firm, freely mobile extra-testicular mass. Most of these epidermal inclusion cysts are reported along the median raphe, from the penis, through the midline of the scrotum, down to the anus. Epidermal inclusion cysts are benign cysts which occur after implantation of epidermal tissue into the dermis or subcutaneous tissues. This implantation can occur from abnormal developmental closure of the median raphe and the urethral groove or secondary to the trauma. Scrotal epidermal inclusion cysts can mimic supernumerary testicle, complex cystic and neoplastic pathologies on USG.

### CASE REPORT

A 42-year-old male presented with painless midline scrotal swelling which was slowly growing over the last few years. There was no previous history of trauma or surgery to that region. On clinical examination, there was a palpable, firm, freely mobile non-tender mass which was separate from both testicles (Figure 1a).

Scrotal USG revealed normal right and left testicles and an additional midline well-defined ovoid lesion with posterior acoustic enhancement measuring 47 x 23 mm (Figure 1b). Lesion was isoechoic to the testicles and devoid of mediastinum testis (Figure 2a). Color Doppler study failed to demonstrate any vascularity within the lesion (Figure 2b).

On surgical excision, intra-operative findings revealed a capsulated mass lesion. Histopathological diagnosis was a benign epidermal inclusion cyst.

### DISCUSSION

Epidermal inclusion cysts are lined by stratified squamous epithelial wall and filled with laminated keratin, cholesterol crystals and debris. These cysts are usually solitary but multiple cysts are seen in Gardner's syndrome. The cysts generally remain asymptomatic unless they rupture, become infected or large enough to cause discomfort with normal function. In our case, the lesion was solitary and painless.

Huang et al conducted a study of sonographic features of 42 surgically proven epidermal inclusion cysts with an emphasis on the pseudotestis pattern. Cysts with sonographic appearance as ovoid lesions with homogeneous low to medium internal echoes were considered in the pseudotestis group. In their study, two-thirds of the epidermal inclusion cysts showed pseudotestis pattern on USG. Our case also showed pseudotestis pattern but lack of internal vascularity and absence of mediastinum testes helped us to reach the diagnosis (Figure 2).

Another study of spectrum of sonographic appearance of epidermal inclusion cysts done by Lee et al, in which they found that most of the epidermal inclusion cysts were ovoid or spherical in shape, associated with posterior acoustic enhancement, avascular on doppler study and hypoechoic lesion with scattered internal echoes was the most common sonographic pattern. In our case, USG findings were in concordance with this study.

MRI is another investigation tool for scrotal lesions evaluation. Epidermal inclusion cyst appears as a well-defined ovoid to spherical lesion, which is hypointense on T1 weighted images, hyperintense on T2 weighted images and shows no internal enhancement on T1 weighted images

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after gadolinium administration.

Although characteristic imaging features of epidermal inclusion cyst have been described on both ultrasound and MRI but possibility of other benign or malignant pathologies cannot be excluded in all cases.

## CONCLUSION

Most of the scrotal epidermal inclusion cysts are benign and asymptomatic. USG imaging appearance of the epidermal inclusion cyst varies with their internal composition and can mimic to the dermoid cyst, complex cyst of the epididymis, malignant mass and supernumerary testis. In our case, lesion was mimicking to the supernumerary testis, however absence of the mediastinum testis and internal vascularity helped to differentiate the epidermal inclusion cyst from the supernumerary testis. Surgical excision is recommended management plan to avoid secondary complication such as rupture or infection and rule out possibility of malignancy.

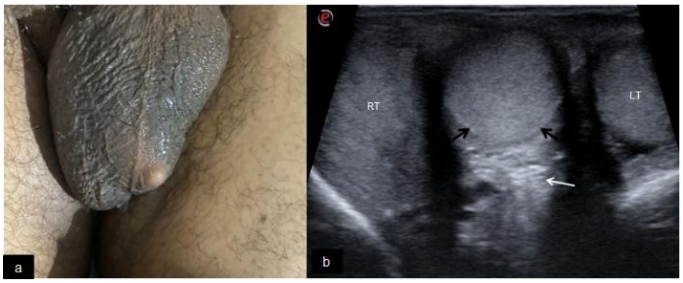


Figure 1: (a) Midline scrotal lesion (b) Grey scale USG image of the scrotum shows normal right (RT) and left (LT) testicles and a midline well defined isoechoic lesion (black arrows) with posterior acoustic enhancement(white arrow).

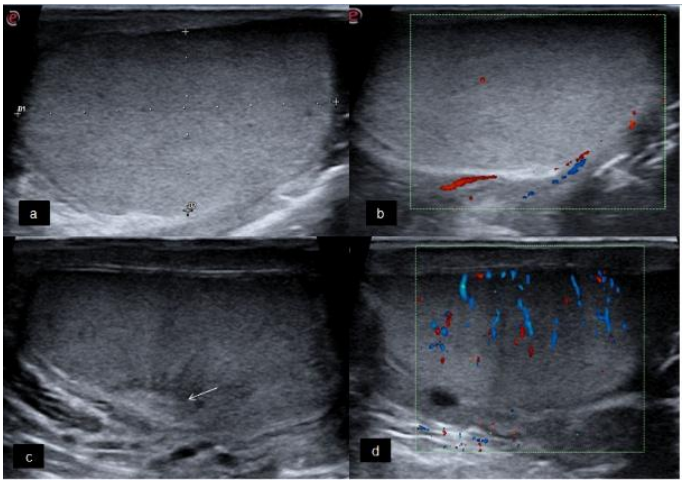


Figure 2: Longitudinal USG images (a & b) of the epidermal inclusion cyst showing absence of mediastinum testis or internal vascularity. Transverse (c) and longitudinal (d) USG images of the normal right testis for comparison showing mediastinum testis (white arrow) and internal vascularity.

## ABBREVIATIONS

USG: Ultra Sonography

MRI: Magnetic Resonance Imaging

## DECLARATION OF ACKNOWLEDGMENT

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## AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are not made publicly available due to concerns of patient privacy and are available from the corresponding author upon reasonable request.

## AUTHORS' CONTRIBUTIONS

Author*: participated in the investigation, conceptualization, methodology, resources, supervision, validation, writing, reviewing, and editing.

Author**: participated in the writing, reviewing and editing.

Author***: participated in writing and editing.

Author****: participated in data collection.

Author*****: participated in follow up of patient.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This case report has been conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from the patient for the publication of their clinical information and any accompanying images. Confidentiality has been maintained throughout the manuscript, with all identifiers removed to protect the patient's privacy.

## COMPETING INTEREST

The authors declare that they have no competing interests.

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## Case Report

# Case Report Hypoplastic Right Heart Syndrome

**Mukesh Mittal*, Pankaj Kumar Nitharwal**, Dinesh Kumar Sahu***, Manju Ghantiyala******


## ABSTRACT

Hypoplastic right heart syndrome (HRHS) is a scarce cyanotic congenital heart disease. Pulmonary valve atresia with an intact ventricular septum is the most frequent right-side defect to cause this syndrome. In HRHS, right side of heart do not function properly and hypoplastic ventricle, hypoplastic or atresia of tricuspid and pulmonary valves and hypoplasia of pulmonary artery cannot send enough blood to the lungs which results in fetal hypoxia and poor postnatal prognosis. HRHS has high perinatal mortality with a very few patients surviving to adulthood without corrective surgery. HRHS is a condition, which demands early diagnostic and surgical intervention in antenatal and neonatal period and intensive postnatal care.

Ultrasound of a 23-year-old primigravida female with 31 weeks of gestation revealed hypoplastic right ventricle, asymmetric heart chambers, ventricle septal defect, narrow pulmonary trunk and pericardial effusion was diagnosed as HRHS and it was confirmed by postnatal 2 D Echocardiography.


**Keywords:** congenital heart disease; antenatal ultrasonography; hypoplastic right heart syndrome.

## INTRODUCTION

HRHS is a rare cyanotic congenital heart disease which presents at birth with under-development of the right side of heart which involves right ventricle, tricuspid valve, pulmonary valve and pulmonary artery leading to right-to-left shunting of the blood through inter-atrial septal defect or inter-ventricular septal defect. Low levels of blood oxygen and cyanosis results from poor blood flow to the foetus due to under developed right side of heart. Hypoplastic right heart syndrome is different from hypoplastic left heart syndrome which involves the underdevelopment of the structures on the left side of the heart. Pulmonary valve atresia is the main anomaly in hypoplastic right heart syndrome. In HRHS child is born without the pulmonary valve. Pulmonary valve is essential for flow of blood from the right ventricle to the pulmonary artery. However, secondary issues associated with hypoplastic right heart syndrome include:

Hypoplastic Right Ventricle- Small right ventricle of the heart pumps less blood to the lungs.

Hypoplastic Tricuspid Valve- The small tricuspid valve causes restriction of blood flow in the right ventricle.

Pulmonary atresia: The pulmonary valve between the right ventricle and pulmonary artery is not formed

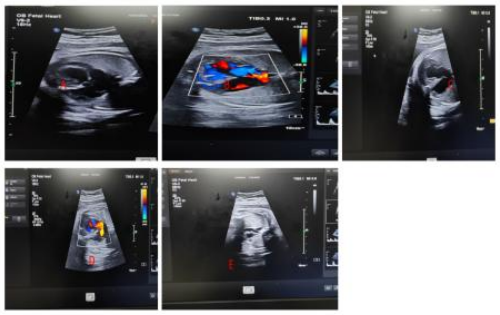
Hypoplastic Pulmonary Artery- Small pulmonary artery results in less blood to the lungs

Blood supply to coronary arteries can be hampered and can results in considerable damage to the heart muscles.

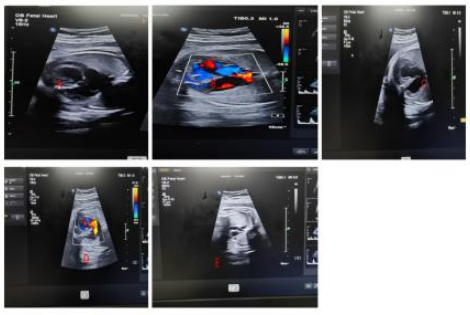
## CASE REPORT

A 23-year-old primigravida female of Indian origin with 31 weeks of gestation presented to our department for routine antenatal sonography. The patient's gestational history, medical and surgical history were unremarkable. Her USG revealed a single live pregnancy of 31 weeks with hypoplastic right ventricle, tricuspid valve atresia, small ventricular septal defect small pulmonary artery, reduce blood flow across the tricuspid valve and normal blood flow across the ductus arteriosus. Fetal heart rate was142 beats/min with regular rhythm.

Fig. 1 Antenatal ultrasound showing



(A) 4 chamber heart view shows small right and left ventricle



(B) Decreased blood flow across the tricuspid valve

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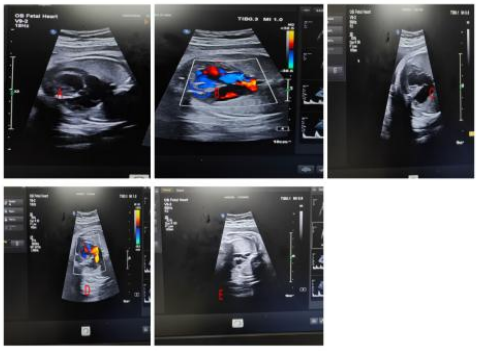
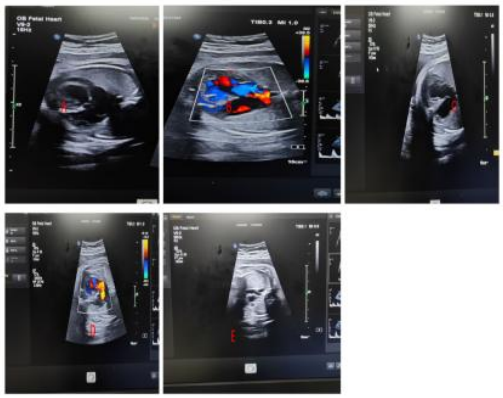
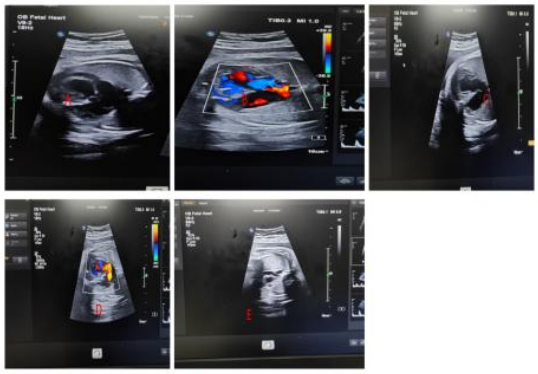


(C) Shows membranous ventricular septal defect



(D) Decreased flow in pulmonary trunk



(E) Narrow RVOT

## DISCUSSION

Antenatal ultrasonography is used as screening test for diagnosis of birth defects and other conditions. Hypoplastic right heart syndrome can be diagnosed in second and third trimester by ultrasonography. Prenatal ultrasound may show a small right ventricle with a small or absent pulmonary artery, with decreased or absent flow through the tricuspid valve and pulmonary valve. This test can show problems with the structure of the heart and how the heart is working with this defect.

HRHS includes following congenital heart defects:

Tricuspid stenosis: The tricuspid valve situated between the right atrium and right ventricle is small.

Tricuspid atresia: The tricuspid valve between the right atrium and right ventricle is not formed.

Pulmonary stenosis: The pulmonary valve between the right ventricle and pulmonary artery is small.

Pulmonary atresia: The pulmonary valve between the right ventricle and pulmonary artery is not formed.

## CONCLUSION

A systematic approach to determine the patterns of associated defects is needed to diagnoses HRHS. Step wise screening is helpful in determining the correct diagnosis of cardiac defect, eighter isolated or associated with other system or a part of syndrome. Early accurate antenatal diagnosis of HRHS by sonography is important so that counselling of patient can be done and early termination of pregnancy can be performed if the patients desires and if patient wants to continue the pregnancy, postnatal management based on the severity of the condition can be done.

## ABBREVIATIONS

USG: Ultra Sonography

HRHS: Hypoplastic Right Heart Syndrome

RVOT: Right Ventricular Outflow Tract

## DECLARATION OF ACKNOWLEDGMENT

The authors have no acknowledgements to mention.

## FUNDING

The authors received no financial support for their research, authorship, and/or publication of this article.

## AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are not made publicly available due to concerns of patient privacy and are available from the corresponding author upon reasonable request.

## AUTHORS' CONTRIBUTIONS

Author*: participated in the investigation, conceptualization, methodology, resources, supervision, validation, writing, reviewing, and editing.

Author**: participated in the writing, reviewing and editing.

Author***: participated in data collection.

Author****: participated in follow up of patient.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

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## COMPETING INTEREST

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## Case Report

# Case Report: Can Placenta Accreta Spectrum be Overdiagnosed in MRI?

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## ABSTRACT

Placenta accreta spectrum (PAS) disorders represent abnormal adherence or invasion of placental tissue into the uterine wall and are associated with significant maternal morbidity. Early and accurate antenatal diagnosis is critical for optimizing maternal and fetal outcomes. Color Doppler ultrasound (CDU) is widely regarded as the first-line imaging modality for PAS, whereas magnetic resonance imaging (MRI) is typically reserved for equivocal cases or for assessing the extent of invasion in advanced disease.

We describe a case of a 32-year-old gravida 5, para 2, abortion 2 woman in her third trimester who was referred with an MRI diagnosis suggestive of PAS. However, detailed CDU evaluation at our institution did not demonstrate features of invasive placentation. Intraoperative findings at delivery confirmed a normally adherent placenta. This case underscores the potential for overdiagnosis of PAS on MRI and reinforces the reliability of CDU as the primary diagnostic tool.


**Keywords:** placenta accreta spectrum; ultrasound; mri; doppler; antenatal diagnosis.

## INTRODUCTION

Placenta accreta spectrum encompasses a group of disorders characterized by abnormal trophoblastic invasion into the uterine wall due to defective decidualization at the endometrial–myometrial interface. This abnormal implantation leads to varying degrees of placental adherence or invasion, particularly in areas of prior uterine injury such as Caesarean section scars.

The spectrum includes placenta accreta (superficial attachment to the myometrium), placenta increta (invasion into the myometrium), and placenta percreta (penetration beyond the serosa, sometimes involving adjacent organs). The incidence of PAS has risen markedly over recent decades, paralleling the increasing rate of caesarean deliveries. Current estimates suggest an incidence of approximately 3 per 1000 pregnancies.

PAS is associated with serious obstetric complications, including severe haemorrhage, disseminated intravascular coagulation, need for hysterectomy, and increased maternal mortality. Despite advances in prenatal imaging, a considerable number of cases remain undiagnosed until delivery.

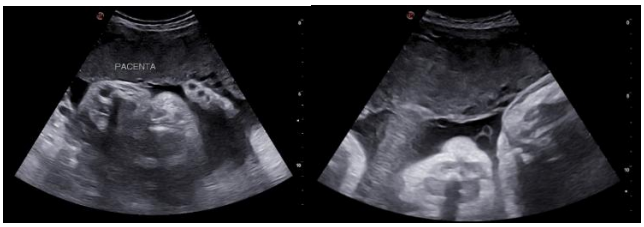
Ultrasound, particularly when combined with CDU, remains the cornerstone of antenatal diagnosis due to its accessibility and high diagnostic performance. MRI serves as an adjunct in selected cases but is not recommended as a routine diagnostic tool according to guidelines from the International Federation of Gynecology and Obstetrics.

## CASE REPORT

A 32-year-old woman (gravida 5, para 2, abortion 2) presented to a tertiary care center during her third trimester for evaluation of suspected PAS. Her obstetric history was significant for two prior C-sections, placing her at increased risk for abnormal placentation.

An MRI performed at an outsourced facility reported findings suggestive of PAS. On presentation to our department, a detailed CDU examination was performed. The placenta was located anteriorly in the upper uterine segment, with preservation of the retroplacental hypoechoic zone and normal myometrial thickness. No abnormal placental lacunae, bridging vessels, or increased vascularity were observed. The bladder–uterine interface appeared intact.

The patient subsequently underwent delivery by C-section, during which intraoperative assessment revealed a normal placenta without evidence of PAS. These findings were consistent with the CDU evaluation and contradicted the prior MRI diagnosis.

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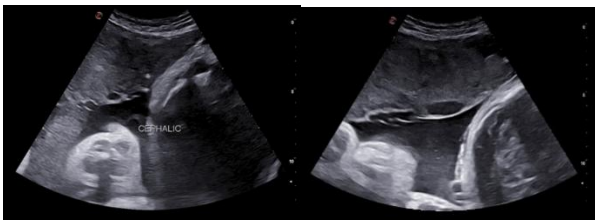


Figure 1: Anterior upper implantation of placenta with normal myometrial thickness and clear retroplacental hypoechoic zone.

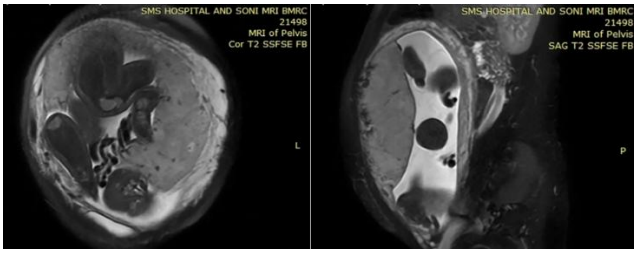


Figure-3 Myometrial thinning at placental bed giving appearance of false positive PAS.

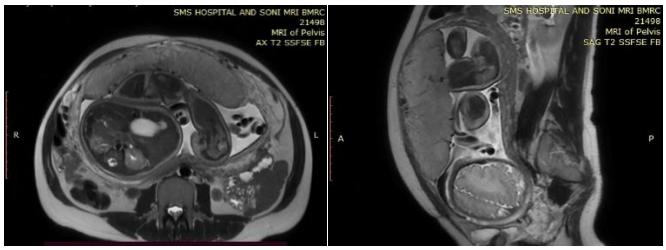


Figure-4 Normal placental bed with normal orientation of vessels in retroplacental zone.

## DISCUSSION

In normal placentation, the decidua basalis acts as a barrier between the placental villi and the myometrium, facilitating separation of the placenta after delivery. In PAS, this interface is disrupted, allowing abnormal adherence or invasion of chorionic villi into the myometrium.

Established risk factors for PAS include prior Caesarean delivery, placenta previa, and other uterine surgeries. The rising prevalence of C-sections has contributed significantly to the increasing incidence of PAS worldwide.

Ultrasound is widely accepted as the primary imaging modality for PAS, with high sensitivity and specificity when performed by experienced operators. Characteristic findings include loss of the retroplacental clear zone, myometrial thinning, placental lacunae, and abnormal vascular patterns on Doppler imaging.

Comparative studies and meta-analyses have demonstrated that MRI does not significantly outperform ultrasound in the diagnosis of PAS. While MRI can provide additional anatomical detail, particularly in complex cases, it is subject to both false-negative and false-positive interpretations.

A false-negative diagnosis is a possibility with MRI caused by the subtle, variable nature of early invasive placental tissue and technical limitations in imaging and MRI alone cannot be used to exclude placenta accrete while a false-positive MRI diagnoses may arise from misinterpretation of physiological changes such as myometrial thinning, placental heterogeneity, or vascular variations. Additionally, technical factors and timing of imaging can affect diagnostic accuracy. Several studies have reported comparable or even superior diagnostic performance of ultrasound compared to MRI. Therefore, current recommendations suggest reserving MRI for selected cases where ultrasound findings are inconclusive or when further delineation of invasion is required for surgical planning.

## CONCLUSION

Placenta accreta spectrum disorders are increasingly encountered in modern obstetric practice, primarily due to rising C-section delivery rates. Accurate antenatal diagnosis is essential for reducing maternal morbidity and mortality.

CDU remains the first-line imaging modality owing to its high diagnostic accuracy and real-time assessment capabilities. MRI should be considered an adjunct tool rather than a primary diagnostic modality.

This case highlights the potential for overdiagnosis of PAS on MRI and emphasizes the importance of correlating MRI findings with ultrasound and clinical evaluation. Careful interpretation of imaging is crucial to avoid unnecessary interventions and optimize patient outcomes.

## ABBREVIATIONS

USG: Ultra Sonography

MRI: Magnetic Resonance Imaging

PAS: Placenta Accreta Spectrum

CDU: Color Doppler Ultrasound

C-section: Caesarean Section

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## AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are not made publicly available due to concerns of patient privacy and are available from the corresponding author upon reasonable request.

## AUTHORS' CONTRIBUTIONS

Author*: participated in the conceptualization, methodology, supervision, validation, writing, reviewing and editing.

Author**: participated in the writing and editing.

Author***: participated in data collection and writing.

Author****: participated in the follow up of the patient.

Author*****: participated in reviewing and editing.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This case report has been conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from the patient for the publication of their clinical information and any accompanying images. Confidentiality has been maintained throughout the manuscript, with all identifiers removed to protect the patient's privacy.

## COMPETING INTEREST

The authors declare that they have no competing interests.

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